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OTFRID FOERSTER 1873–1941

AN APPRECIATION

On August 11th, 1941, word reached the United States via Switzerland that Professor Otfrid Foerster had died in Breslau, Germany, on June 15th. Dr. Foerster had written to us during the preceding winter from a sanatorium in Switzerland, where he and his wife were both ill with tuberculosis. Frau Foerster survived her husband for only one day. A letter from his sister says: "So, they have both been buried together. All Breslau took part in the burial. There was a speech of the Protestant clergyman first, then: the Rector of the University, a representative of the town council, his successor Professor von Weizsäcker, who had come from Heidelberg at Easter (Internist); then two doctors from Hamburg and Frankfurt, finally the Oberarzt Dr. Stender. They all praised Otfrid's value to the utmost and the appreciation of him was really marvelous. At the last came the Roman Catholic priest for Marthe."

To the many neurologists, neurosurgeons, physiologists and anatomists of the English-speaking countries, who have been to Breslau in the past twenty years, this description will recall much of the city, the hospital and the associates which form the background of a man who had become the foremost teacher and most learned authority in the field of the neurological sciences and one of the strongest personalities of his time in medicine.

Otfrid Foerster* was born at Breslau, November 9th, 1873. His early years were spent at Kiel where his father held the chair of Philology, but he later had schooling at the gymnasium at Rostok and at the Maria Magdalene Gymnasium in Breslau receiving his diploma in 1892. Between 1892 and 1896 he studied medicine at the Universities of Freiburg, Kiel and Breslau, taking his state medical qualifications at Breslau during the winter semester of 1896–97. His inaugural dissertation entitled *Quantitative Untersuchungen ueber die agglutinirende und baktericide Wirkung des Blutserums von Typhuskranken und-Reconvalescenten* written at Breslau, was defended on May 20th, 1897.

This dissertation is the only paper published by Foerster† which was not directly connected with matters of the nervous system. During his student years he had spent some months in the Psychiatric Hospital at Lüben where Kraepelin had first worked and he had come under the influence of Wernicke in the Medical School at Breslau. At the suggestion of the latter, he went in 1897 to Paris and remained there for two years as a pupil of Déjérine, attending at the same time the clinics of Pierre Marie, and of Babinski. The summers of these years were spent at the clinic of Professor Frenkel in Switzerland, and in 1899 he was sent to the United States to demonstrate

* In his early life Dr. Foerster spelt his given name "OTFRIED." In 1903 he dropped the 'e' and adopted the spelling of OTFRID.

† A complete list of Dr. Foerster's writings follows this appreciation.

Frenkel's new "Uebungstherapie" for tabes. His memories of this early trip were always vivid; he stayed in Tarrytown with an American gentleman who was representative for a firm buying French and German wines, and it was here, he recalled, rather than in Germany that he learned about the Rhenish wines; here also he met John D. Rockefeller, senior, who, Foerster related, spoke excellent German. Just before his return to Paris he visited Washington and, because funds by then were low "and because I liked them," he lived for some days on bananas! In 1899 he returned to Breslau and entered the Clinic of Wernicke where he collaborated with him in his published *Atlas* of brain sections issued in 1903.

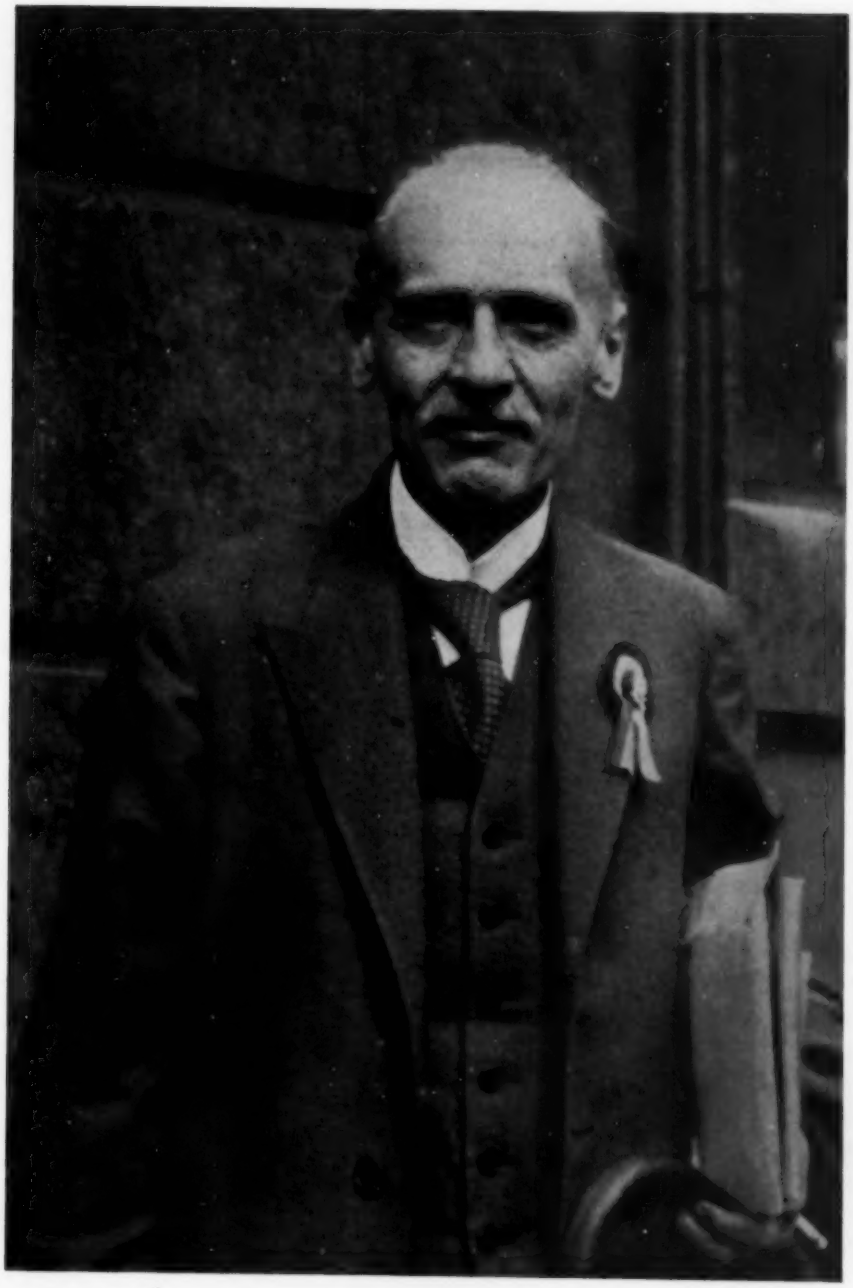
His extraordinary memory and ability to apply and order his knowledge were early recognized; it was said that as a boy and young man his knowledge of botany, geology and other natural sciences was remarkable. An accomplished linguist, schooled by his father in the use of words, he had learned to read, speak and write faultless English as well as French and Italian and he had a fair grasp of Polish, Russian and the Scandinavian languages.

About 1905 he began to study the English neurophysiological literature, beginning with David Ferrier and following through Beevor, Horsley, Schäfer and, finally, Sherrington who, as he often said, influenced his thinking more than any other writer. Students who went to Breslau often saw a well-worn copy of *The integrative action of the nervous system*, and he had read and closely analyzed all of Sherrington's later papers. When Prof. E. G. T. Liddell, who with Sherrington had first described stretch reflexes, met Foerster in 1930, Foerster remarked that their papers on the myotatic reflex had clarified for him one of the principal problems of neurology.

His study at home where all his writing was done (before 11 A.M., when he went to the hospital, or late at night), contained the books for which he cared most. They were notably few: the complete works of Helmholtz, Goethe and Schiller, the collected works of Hughlings Jackson, Sherrington, and Harvey Cushing. But his reprints were beyond counting. They lay in large and apparently chaotic piles on tables, shelves and on the floor. But it only took him an instant to find among them the particular reference which he might need to illustrate a point.

The chronological sequence of his three hundred published works, given in the bibliographical list which follows, will indicate the progression and order of his work, the breadth of his knowledge and the tremendous industry which enabled him, an active clinician and a surgeon with a private practice, to pursue investigations and to write (always in his own hand), such compendia as are represented by his articles in the *Handbuch der Neurologie*.

Throughout the forty years of his active professional life one perceives two dominating characteristics: his power of observation and analysis, and his capacity to apply fundamental knowledge toward the relief of symptoms —this at a time when clinical neurology was still under the influence of the purely diagnostic schools of Paris and of Queen Square, and before the era



OTFRID FOERSTER

of neurosurgery. In this field of neurology where therapy had been often unconsidered, Foerster's physiological insight led directly to the use of surgery, in the relief of intractable pain through chordotomy, and of spasticity through dorsal root section. His analysis of the distribution of the sensory dermatomes arose from his use of the latter procedure. Diagnosis of cortical tumors and of focal scars in epileptics by stimulation and subsequent ablation, under local anesthesia, led to his equally fastidious analysis of functional localization in the cerebral cortex. These and his clinical studies on basal gangliar disease all bear the mark of an originality and courage almost without parallel in clinical medicine.

Before the onset of the first world war he had as neurologist directed the surgeons, Tietze and Küttner, in the execution of surgical procedures. In 1914 when general surgeons had become scarce, he began, although more than forty years of age, to do his own neurosurgery. Self-made as a surgeon he always lacked refinement of technique, but his results were surprisingly good because of his remarkable speed and manual dexterity. Although hemostasis and even asepsis were often crude, the operations for nerve sutures and cord sections were carried out as perfect anatomical dissections.

After the last war Foerster published many papers on war injuries, and then by logical progression, and through fortunate association with Gagel as neuropathologist and Altenburger as neurophysiologist, the bulk of his work was diverted into diagnosis of cerebral tumors and to electrophysiological analysis. The neurosurgical operations in his hospital were done by Dr. Stender during the last few years, although Professor Foerster remained Director of the *Neurologisches Forschungsinstitut* until 1941.

He was as remarkable a teacher and leader as he was physician. For many years as President of the *Gesellschaft deutscher Nervenärzte*, his opening addresses were masterpieces of descriptive history of the development of German medicine. His lectures, into which he put much time and great effort, were models of clarity and precision in whatever language he happened to be speaking. His presentations were always highly illustrated as were his published works. We have known him to show as many as 160 lantern slides during a single lecture, their sequence being unfailingly memorized and the order of his thought undisturbed by their presentation.

His contacts with other countries were extensive. He visited the United States four times: first in 1899, as above mentioned, and then in 1912 when he addressed the American Association of Physicians and Surgeons at the instigation of Franklin Martin. In 1914 he came again and spoke before the American Medical Association at Atlantic City. His fourth visit was in 1930. From a distance he had long admired the work of Harvey Cushing, and when asked by Dr. Cushing to act as Surgeon-in-Chief *pro tem* at the Peter Bent Brigham Hospital in Boston, he immediately accepted. The result of this exchange was far-reaching and both Cushing and Foerster referred to it in later years with particular satisfaction. Foerster went frequently to England, and in 1937 the Society of British Neurological Sur-

geons, which includes in its membership many neurosurgeons of continental Europe, held its annual meeting in his Neurological Institute (now renamed 'Otfrid Foerster Institut') at the Wenzel Hanke Krankenhaus in Breslau.

During Professor Foerster's last years his work was restricted to some degree by increasing tension within his country. He was under surveillance both because he had for a time been physician to Lenin in Moscow, and because his wife was partly Jewish. By 1936 he, with many others, ceased subscribing to all journals outside Germany, and in 1938, when he was asked to represent German clinical neurology and neurophysiology on the Advisory Board of this *Journal*, he felt unable to accept the appointment.

Yet for the fifteen years preceding 1939 students from the United States, Great Britain, Canada, Australia, South America, China and Japan; from Scandinavia, Rumania, Holland, France and Italy had found in remote Breslau a man already cognizant of all that was significant in neurology in each of their countries, and one who was usually personally acquainted with their leaders. From him they gained much factual knowledge and much of the history and development of their science. They saw a neurosurgeon self-trained in surgery; a neurologist with few equals in his knowledge of anatomy and physiology; a gifted teacher,—master of many languages,—and artist in the use of his own, and a physician who inspired a deep sense of personal devotion in his patients and students. They returned to their homes, deeply influenced by contact with this man whose life had been inflexibly shaped and disciplined to follow one ideal and who, through incessant effort and through rigid economy of time, and even of friends, has left an indelible impression on the clinical neurology of this generation.

M. A. K.
J. F. F.
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* Copies of this can be found in the libraries of Dr. John F. Fulton, Yale University School of Medicine, New Haven, Connecticut, Dr. Paul C. Bucy, Chicago, Illinois, and Dr. C. G. de Gutiérrez-Mahoney, Vanderbilt University School of Medicine, Nashville, Tenn.

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ELECTRIC POTENTIAL CHANGES AT AN ISOLATED NERVE-MUSCLE JUNCTION

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IN RECENT studies of neuromuscular transmission one of the main difficulties was the scatter of the nerve-muscle junctions. This was partly overcome by using a strip preparation of the cat's soleus (cf. Eccles and O'Connor, 1939) which contains nerve-muscle junctions restricted to 1–2 mm. of muscle length. Further investigations (Eccles, Katz and Kuffler 1941a, b; Eccles and Kuffler 1941a, b) were done on this strip-preparation and on frog sartorius which contains discrete foci of nerve endings (Katz and Kuffler, 1941).

Although a sharp focus of nerve-muscle junctions would give an electric response similar to that of a single element, there are obvious advantages in recording from an isolated single neuro-muscular junction. The main objects of this investigation on the isolated nerve-muscle fibre preparation (cf. Kuffler, 1941) are (i) to record the potential change at the small area of the junction itself, as distinct from the rest of the fibre; (ii) to find the relationship of this potential to the origin of the muscle spike potential.

METHODS

Different muscles in frog (*Hyla aurea*) were tried, such as M. glosshyoideus, the leg-skin muscle, M. semitendinosus and other leg-muscles. Finally the M. adductor longus was found the most suitable. This muscle is 2–3 cm. long, has parallel fibres about 80μ in diameter and comparatively little connective tissue.

The muscle is removed with 2–3 cm. nerve attached and put into a glass-chamber filled with saline. This chamber is placed on a microscope stand with both direct and transmitted illumination. The dissection is done under a binocular microscope and a magnification of 10–30 is used. During the whole dissection the muscle is kept in saline while the tendinous ends are gripped by screw-adjustable forceps which hold the preparation taut. With M. adductor longus the proximal end is left attached to the insertion at the symphysis. After removing the connective tissue sheath with fine scissors the muscle is dissected with thin needles and silver-steel knives with fine edges and sharp points. The course of the nerve down to its finer branches can be followed up easily and all muscle fibres are removed except those innervated by one of these fine branches. When about 10 fibres are left in a muscle-bundle, fibre after fibre is dissected away, care being taken not to injure the nerve, until eventually a single muscle fibre is left with its innervation intact. (Microphotograph Fig. 1.)

As a rule the fibre need only be dissected clean over a few millimeters each side of the nerve entry. Slight injury of the muscle fibre such as touching with the needle, excessive pulling when freeing it from adjacent muscle fibres and connective tissue will damage the fibre easily and render it inexcitable in a few minutes. Such an injury can be seen under the microscope and at these places the protoplasm retracts from the sarcoplasma, becomes opaque and seems to break up. The injury spreads very quickly along the muscle fibre.

Two methods of recording were used. (i) The fibre was either lifted up into paraffin floating on the saline (Hodgkin, 1938) or (ii) was brought up to the saline-paraffin interface where the recording was done while the nerve was stimulated in the overlying paraffin. This latter method had the advantage that drugs such as curarine could easily be applied to the preparation through the saline and there was better contact between recording electrode and fibre, because this was pressed against the electrode by the interfacial tension of the saline-paraffin junction. As shown in Fig. 2 the muscle fibre was lifted up so as to

protrude into the paraffin while still remaining surrounded by a thin film of saline, i.e. without breaking at any point the paraffin surface. In Fig. 2. a fine film of saline should be shown between the fibre M and the paraffin P. With successive movements of the electrode the interface position with regard to the muscle fibre is unaltered. One leading electrode thus made contact with the fibre, while the other lead was kept in the saline, forming a large indifferent lead. Small movements (50–100μ) of the leading electrode along the muscle fibre were made by means of a micrometer adjustment under direct microscopic observation. Accurate electrode shifts were only possible when the muscle fibre had been freed from loose connective tissue.

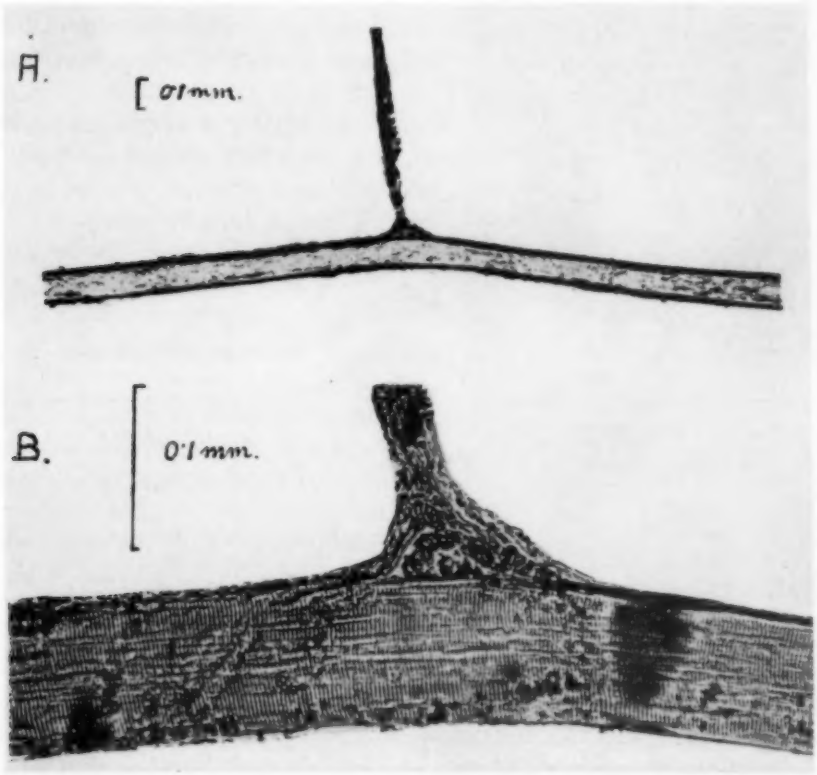

FIG. 1. Microphotograph of a living single muscle fibre with its nerve supply. A, lower. B, higher magnification. Dark area to the right of the nerve-entry is a small air-bubble.

In frog's muscle the end-plate extends over about 100μ fibre length, hence in order to record selectively from such a region, the recording electrode must make a very good and accurate contact and it must be insulated elsewhere. This was done most effectively by embedding a platinum wire of 50μ diameter in a fine glass hook (about 300μ thick), so that only a small area of the platinum was uncovered on the inner side of the angle of the hook. When the hook pulls the muscle up at the paraffin-saline interface the platinum electrode will thus make a good contact with a small area of the muscle while the surrounding glass will largely prevent it from leading from adjacent regions of the muscle (Fig. 2).

A single nerve-muscle fibre preparation survived under experimental conditions in the interface for 6–8 hours and sometimes was kept as long as 24 hours without appreciable deterioration. Isolated single muscle fibres, without their innervation, have been kept in Ringer by Ramsay and Street (1941) up to ten days and gave normal propagated twitches if stimulated directly. In paraffin the muscle fibre frequently ceased to conduct after 1–2 hours. So far 25 successfully dissected preparations have been experimented on.

The stimulating and recording apparatus was the same as described by Eccles, *et al.* (1941b). For recordings in paraffin a preamplifier of low input capacity was added, so as to minimize distortions arising on account of the high input resistance. A rectangular input through a 2 MΩ input resistance then reached 90 per cent deflexion in 0.15 msec.

Results

A. The action potential at the nerve-muscle junction and some distance away from it

For recording from the single fibre in the interface similar conditions obtain as with the 'strip'-preparation of the cat (cf. Eccles and O'Connor, 1939, p. 49), or with an active nerve fibre in a large volume of a conductive medium (Bishop, 1937).

Figure 3a shows an action potential set up by a single nerve impulse when, using microscopic observation, the recording electrode is placed on

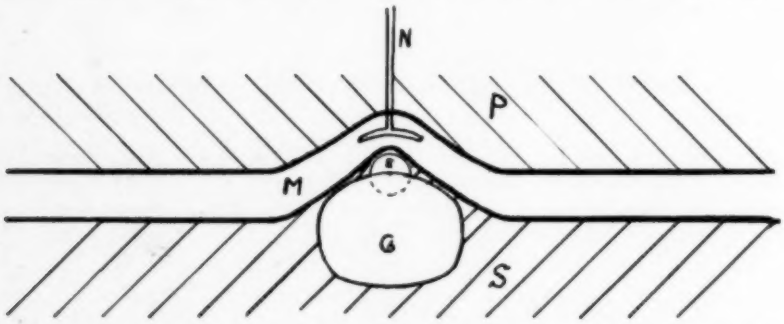

Fig. 2. The recording system at the paraffin-saline interface. P, paraffin oil; S, saline; G, glass rod (shown in transverse section) in which the platinum wire electrode E, is embedded; M, muscle fibre; N, nerve.

the neuro-muscular junction (n.m.j.). The potential rise is composed of two phases. The first component rises in about 0.5 msec. to 90 per cent total potential height, and the second smaller part follows after a slight delay. When the recording electrode is moved 80μ away (Fig. 3b), the latent periods of the two components are not appreciably altered, but the first is smaller and the second shows a larger rising phase. This differential effect on the size of the two components is much increased by a further movement to 230μ from the n.m.j. (Fig. 3c), and in addition the peak of the second component is delayed by 0.3 msec. Recording at progressively larger distances from the n.m.j. shows a corresponding increase in this delay. The spike-like second component is thus shown to be due to a propagating muscle impulse, the speed of propagation being about 2 m. per sec. On the other hand the latent period of the initial potential is not altered when recorded 80 or 230μ away from the junction, but its rate of rise is diminished. This indicates that it is due to a local potential generated at the n.m.j. and spreading from there electrotonically along the muscle fibre.

At 0.5 mm. distance (Fig. 3d) from the n.m.j. the initial potential is inversely recorded, while the negative phase of the spike is preceded by a

quick positive wave. Similar findings were obtained in the cat (Eccles and O'Connor, 1939; Eccles *et al.*, 1941b) and are due to the leading conditions (see above). The initial positive deflexion makes it difficult to interpret accurately potentials recorded some distance from the n.m.j.

Thus it is evident from Fig. 3a, b, c, d, that a nerve impulse sets up a potential at the n.m.j., the "end-plate potential" (henceforth e.p.p.), which reaches its peak in about 0.5 msec. and decrements very rapidly along the muscle fibre. No accurate data about this electrotonic decrement can be given owing to distortions due to the leading conditions (but see Fig. 3). The rapid spatial decrement would be expected for the electrotonic spread of such a brief potential change (cf. Bogue and Rosenberg, 1934).

In the earlier experiments potentials similar to Fig. 3c were usually recorded at the n.m.j. However, with improvement of the dissection technic the muscle fibre was freed from nearly all surrounding tissue and it was possible to obtain a much better contact of the recording electrode. Under such conditions and with careful placing of the electrode right on the motor endplate it was often found that the e.p.p. was so large that no spike could be detected rising above it (Fig. 3e).

The potential changes beyond the spike summit (cf. Fig. 3 and later figures) cannot be interpreted until the interaction with antidromic muscle impulses has been investigated.

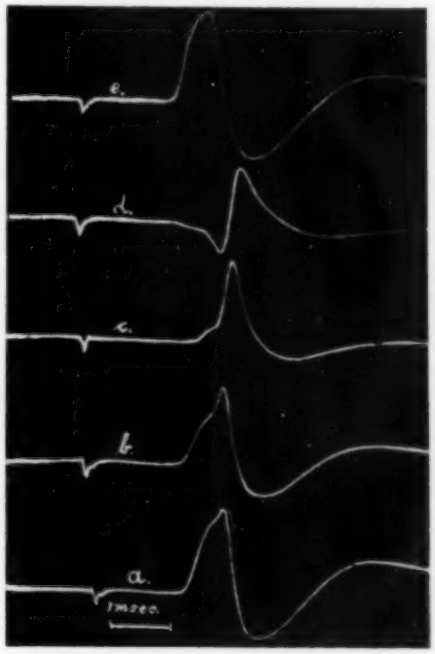

FIG. 3. Recording at different positions on the muscle fibre. a, at the nerve muscle junction; b, c, and d, at 80, 230 and 500μ distance from the junction. e, after careful placement of the electrode on the end-plate, no spike action potential is observed (see text).

The simplest way of recording from a single muscle fibre would be in paraffin oil, as was done by Hodkgin (1938) for single nerve fibres. However two main difficulties have not yet been overcome. (i) In the absence of interfacial tension, the fibre is not pressed against the electrode and, therefore, the contact is not well defined. Moreover, when the preparation is lifted into paraffin, some saline still adheres to it especially round the nerve entry, forming a drop of varying size. (ii) Little droplets along the fibre probably account for "false-leads" which complicate the records by introducing small diphasic waves similar to those described by Bishop, Erlanger and Gasser (1926) and Bishop and Gilson (1929). This latter difficulty could frequently be overcome by keeping the recording leads close together.

Figure 4a shows an observation at the n.m.j. in which the initial e.p.p. attains only about 40 per cent of the total action potential height. Figure 4b is a record taken in the interface at a comparable position. The relative sizes of the e.p.p. and spike and the periods of rise are not appreciably different from Fig. 4a, though as a rule the time course was a little slower in paraffin. Thus it appears from the recordings in paraffin, that the rising phase at the n.m.j. is not appreciably distorted when leading at the paraffin-saline interface. Action potentials up to 100 mV have been obtained in paraffin.

B. THE ACTION OF CURARINE

Curarine was added to the saline-bath so that it reaches the preparation after gradual diffusion. In this way it usually took 20–30 min. to exert its full effect on the junction. During this time action potentials could be recorded at various stages of curarization as shown in Fig. 5 and 6. A final concentration of 1–2μ mol per l. of curarine chloride is generally sufficient for a complete block of neuromuscular transmission.

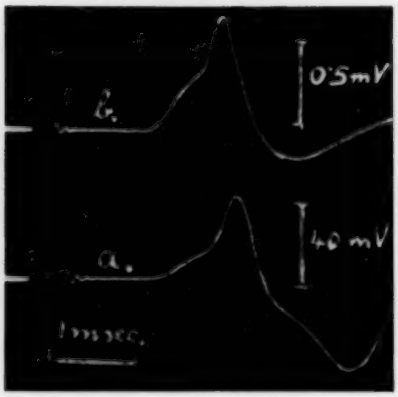

FIG. 4. a, diphasic action potential at the end-plate region, recorded in paraffin oil; b, action potential recorded in the interface with corresponding position of the recording electrode. Note the difference of potential scale: 40 and 0.5 mV. respectively.

Figure 5 shows a series of observations during curarization where the recording electrode is placed as near as possible to the n.m.j., the e.p.p. reaching a little over 70 per cent total potential height (Fig. 5a). The main actions of curarine are seen to be (i) progressive diminution of rate of rise and total height of the e.p.p., but no appreciable effect on its latent period; (ii) a progressive delay in the latent period of the spike, but no significant change in its height; (iii) finally as shown in Fig. 5e disappearance of the spike, leaving behind a pure e.p.p.

Thus the initial e.p.p. can be diminished from over 70 per cent total potential height in Fig. 5a to about 40 per cent in Fig. 5d and still a spike arises. With a slight further diminution (compare Fig. 5d and e), the absence of a spike shows that no propagated muscle impulse is initiated.

In all experiments where an e.p.p. of over 90 per cent total potential height was obtained, the e.p.p. diminished to 40–50 per cent during subparalytic curarization. Together with the reduction of the initial e.p.p. the residual end-plate negativity after the spike is greatly diminished, suggesting that in the non-curarized muscle, part of the e.p.p. outlasts the spike (cf. Eccles and Kuffler, 1941b). The time course of this surviving e.p.p. cannot be established accurately from the recordings in the interface.

As would be expected, once the spike is set up, it reaches an absolute height similar to the pre-curarine state, but variations within 15 per cent have been observed. In some experiments the latent period of the e.p.p. also varied, while no temperature change occurred. This is possibly due to

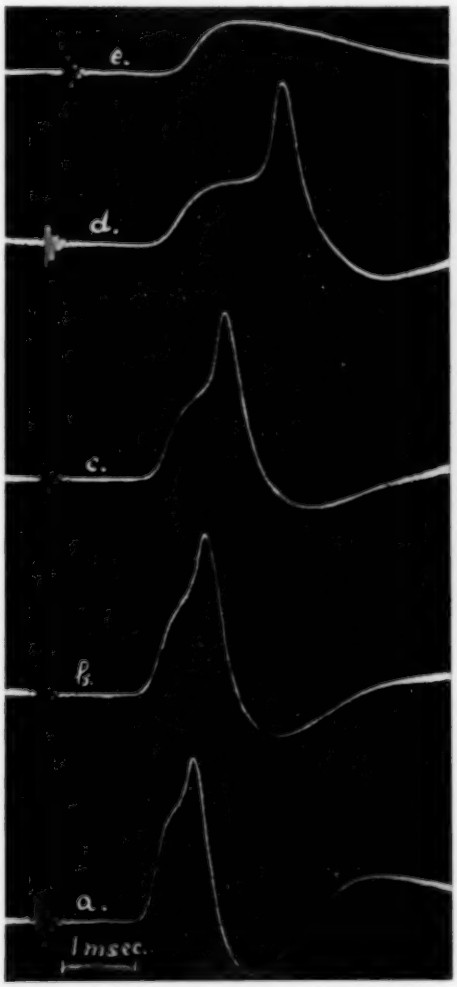

FIG. 5. Records taken at the end-plate region. a, before application of curarine; b, c, and d, during progressive curarization show the diminution of the initial end-plate potential (e.p.p.) and the progressive lengthening of the spike latent period; e, pure e.p.p., no spike is set up.

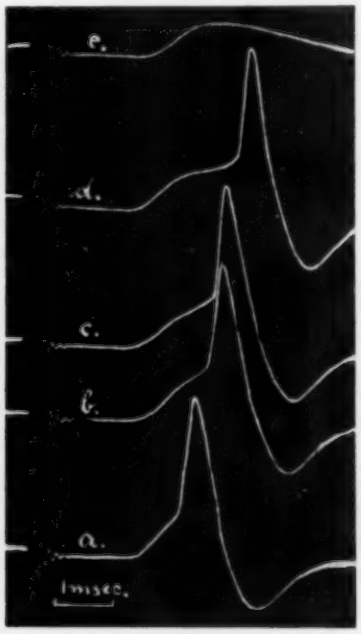

FIG. 6. Progressive curarization as in Fig. 5, some distance from the end-plate. a, before application of curarine; b, c, and d, show practically no change in e.p.p. height at the spike origin; e, pure e.p.p.

slowing of the conduction rate of the nerve impulse during curarization.

Figure 6 shows another set of observations during the application of curarine. The recording electrode was moved a little away from the endplate so that an initial e.p.p. of about 30 per cent total spike height was recorded. A striking difference from Fig. 5 can be seen in the curarine effect. The height of the e.p.p. at which the propagated impulse starts is not appreciably changed during progressive curarization, while all the other effects of cura-

rine are similar to those described above. Experiments of this type were done in six preparations in which the initial e.p.p.'s were normally only 20–30 per cent total potential height. The change observed during curarization never exceeded a few per cent.

Discussion

It is at first surprising that the end-plate potential (e.p.p.) preceding the spike could not be found in the multifibre preparation of the isolated frog's sartorius (Eccles *et al.*, 1941a). Its occurrence in each single nerve-muscle fibre preparation is beyond doubt and the fact that these fibres gave consistent results for over 6–8 hr. while being frequently stimulated and manipulated suggests that they are in a good condition. However, these experiments have shown that very localized leading from the end-plate zone is necessary in order to detect the e.p.p. This does not seem possible in the whole muscle, where the aggregate potential from the scattered end plates would not show the sharp change in curvature which separates the e.p.p. and the spike in a single fibre.

Despite its close resemblance to the single fibre potentials, the double-step potential described by Schaefer and Haass (1939) could not have been due to an initial e.p.p. preceding the spike. Presumably it is produced by spikes in two different sets of muscle fibres as has already been suggested (Eccles *et al.*, 1941a). In the strip-preparations of cat's soleus a large initial e.p.p. (12–18 per cent peak-potential) was sometimes observed preceding the spike, but usually it was much smaller or even undetectable (cf. Eccles and Kuffler, 1941a).

There has been previous evidence (Eccles and O'Connor, 1939; Eccles *et al.*, 1941a; Schaefer and Haass, 1939) that the e.p.p. is responsible for initiation of the propagated spike when a subparalytic dose of curarine is applied, or during the refractory period. From the preceding experiments it is clear that the e.p.p. is also normally responsible for the initiation of the propagated muscle action potential. In most experiments an e.p.p. of 90 per cent total action potential height was found, and in many cases the e.p.p. formed the entire rising phase of the action potential at the end-plate (cf. Fig. 3e), the only sign of a propagated spike being the following diphasic part of the potential. It seems reasonable to suggest that e.p.p.'s at least as large as the spike potential are produced in all preparations but are not fully recorded on account of the relative smallness of the endplate and the difficulty of placing the electrode exactly on it. Moreover the end-plate does not reach round the whole circumference of the muscle fibre.

It would be of interest to know the threshold e.p.p. required for the initiation of a propagated impulse. Direct evidence might be obtained by recording at the exact position where the impulse starts; there the shortest spike-peak time would be obtained. For that a still finer method of leading would be necessary, but is not feasible at present. Further, the electrode shifts as a rule can be màde in a longitudinal direction only, although rota-

tion of the fibre has been attempted. The absence of a spike component in Fig. 3e suggests that the spike arises some distance away from the point of recording. It would seem that the e.p.p. has to spread and depolarize the surrounding region sufficiently to set up a propagated impulse. This would be further supported if a point could be found near the end plate, where the spike starts whenever the e.p.p. reaches a given height. Indirect evidence on this point was obtained by the curarization experiments (cf. Fig. 6).

At the end plate (cf. Fig. 5d) the e.p.p. diminished to about 40 per cent potential height before the spike was abolished; the height of e.p.p. and spike initiation were apparently unrelated. At a little distance away, however (cf. Fig. 6), the spike seemed to take off from an approximately constant level of the e.p.p.; about 30 per cent of full spike height. The spike latency naturally increased with progressive curarization as a longer time was now required for the e.p.p. to reach the critical potential height. No spike appeared when the e.p.p. was slightly reduced (cf. Fig. 6d and e). This would suggest that the propagation along the muscle fibre starts whenever the region adjacent to the end plate is depolarized to about 30 per cent of the spike height.

From six experiments of this kind (as Fig. 6) it seems likely that the threshold level is about 30–35 per cent of the total action potential height.

The foregoing experiments show that the end plate itself has some different properties, regarding its excitability, from the rest of the muscle. A potential appreciably greater than necessary to initiate propagation at another point of the muscle fibre, can be set up without immediately propagating itself. Hodgkin's (1938) findings for nerve thus appear to obtain for the regions adjacent to the end plate, but not for the end plate itself.

As pointed out above, latency changes of e.p.p. rise during curarization were sometimes observed. These changes, if also occurring in cat, might explain the failure of Eccles and Kuffler (1941a) to obtain a similar time course of the e.p.p. and initial part of the spike in the "matching" tests, done on curarized preparations. Therefore the possibility of a quicker transmitting process than the e.p.p. could not be excluded in the cat experiments.

In the light of the present findings a still quicker mechanism for neuromuscular transmission need not be postulated for the single fibre preparation of the frog.

Summary

Single muscle fibres with their nerve supply have been isolated from the M. adductor longus of frog (*Hyla aurea*). Electric potential changes have been recorded at the nerve-muscle junction.

1. A potential of about the same size as the muscle spike potential is set up by the nerve impulse at the endplate, the end-plate-potential (e.p.p.).

2. This e.p.p. is responsible for the initiation of the propagated muscle impulses.

3. The e.p.p. can be greatly diminished by curarine before the spike is abolished.

4. There is evidence that the e.p.p. gives rise to the muscle spike by spreading electrotonically and critically depolarizing the region adjacent to the end-plate. It is suggested that the threshold for the initiation of a propagated impulse is about ⅓ of the normal e.p.p. height.

I wish to thank Dr. J. C. Eccles and Dr. B. Katz for their valuable help and assistance during the course of this investigation, and also the National Health and Medical Research Council of Australia for equipping and maintaining the workshop in which most of the apparatus was made.

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RESPONSES OF THE IRIS TO PROLONGED STIMULATION OF ITS PARASYMPATHETIC NERVE SUPPLY*

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ORIAS (1932) reported that stimulation of the preganglionic sympathetic fibers at relatively high frequency failed to elicit a sustained contraction of the nictitating membrane. When the postganglionic sympathetic fibers were stimulated under the same conditions the response of the membrane was maintained for long periods.

Lanari and Rosenblueth (1939) confirmed Orias' observation, and found in addition that prolonged continuous stimulation (2 to 3 hours) of the postganglionic sympathetic fibers resulted in a slow decline of the contraction of the nictitating membrane and of the dilator muscle of the iris. Stimulation of the preganglionic sympathetic fibers resulted in a more rapid decline of response (4th stage) followed by a late persistent increase (5th stage). A similar late increase of response took place when the vagal preganglionic parasympathetic nerves to the heart were stimulated. The 4th and 5th stages have also been observed during prolonged indirect stimulation of skeletal muscles (Rosenblueth and Luco, 1939).

The 4th and 5th stages appear, therefore, when sympathetic or parasympathetic preganglionic nerve fibers, or when motor nerve fibers are stimulated. All these nerves are cholinergic. The 4th and 5th stages, on the other hand, are not present during the stimulation of adrenergic postganglionic sympathetic fibers.

These data suggested the following questions. Is that difference in results due to the different nature—cholinergic or adrenergic—of the nerves? Or is it because in the first instance a ganglionic or a neuromuscular synapse is involved, while in the negative case the transmission occurs across a postganglionic smooth-muscle junction?

To answer these questions it was considered necessary to stimulate cholinergic postganglionic parasympathetic fibers and record the contraction of the smooth muscle innervated by them. The postganglionic fibers of the ciliary ganglion (short ciliary nerves) were selected, for three reasons: *a*, they are readily accessible; *b*, they are compact; and *c*, they form a relatively large bundle. The pupillary diameter was used as an indicator of contraction. The short ciliary nerves contain, however, some sympathetic fibers. It was necessary, therefore, to remove the superior cervical ganglion and wait for the degeneration of these fibers in order to test the effect of the parasympathetics alone.

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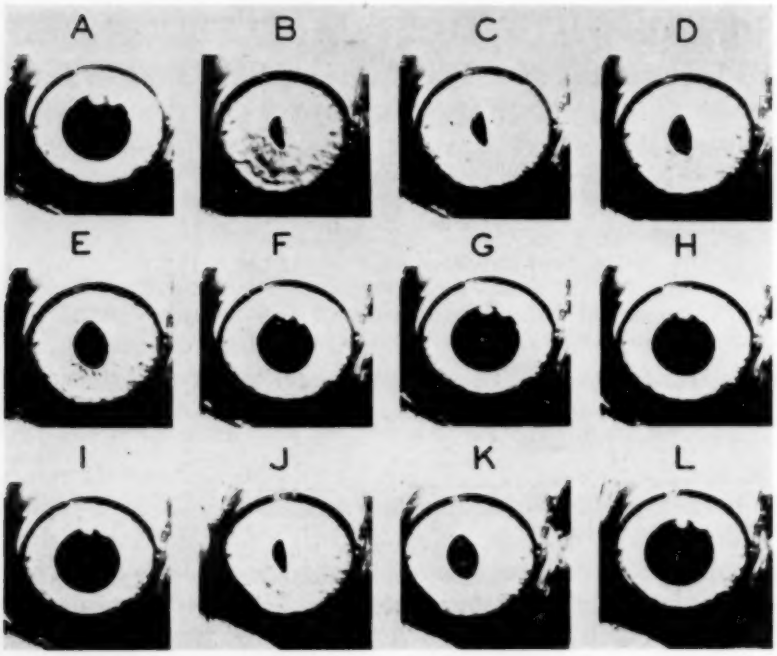

FIG. 1. Influence of frequency of stimulation of postganglionic parasympathetic fibers on responses of the iris. The superior cervical ganglion had been removed 10 days previously, to eliminate the sympathetic component of the short ciliary nerves. The stimuli were applied for one minute and the periods of stimulation were separated by 2-minute intervals. Photographs were taken 15 and 60 seconds after the beginning of stimulation; the pupillary diameter was practically the same at these times.

A, G and L are controls without stimulation. The other records are responses to different frequencies of stimulation as follows: B, 25; C, 50; D, 75; E, 100; F, 150; H, 200; I, 300; J, 25; and K, 17 per sec.

As a control for these observations some experiments were made in which the preganglionic parasympathetic fibers to the iris were stimulated in the IIId cranial nerve.

METHOD

Cats were used under dial anesthesia (Ciba 0.75 cc. per kg. intraperintoneally). To isolate the parasympathetic fibers it was necessary to remove a portion of the external wall of the orbit. Some of the external muscles of the eye were cut away and the ciliary nerves were dissected. The stimulating electrodes were placed beyond the location of the accessory ciliary ganglion which exists occasionally, lying distal to the ciliary ganglion (Whitteridge, 1937). When possible both the lateral and the medial short ciliary nerves were included within the electrodes. Often, however, it was not possible to use both branches. In those cases the main branch (lateral) was used alone (for the anatomy of this region see Whitteridge, 1937).

For stimulation of the preganglionic parasympathetic fibers in the IIId nerve the preparation was as follows. The external carotid on the unused side was ligated. The cervical sympathetic was cut bilaterally. After opening the skull a hemidecerebration was performed on the side which was to be stimulated. Electrodes were then placed on the exposed IIId nerve. Continuous suction by vacuum pump prevented the collection of cerebrospinal fluid or blood around the electrodes.

The pupillary changes were recorded either by measuring its transverse diameter or by photographing the eye at different times during stimulation. The stimuli were con-

denser discharges through a thyratron, controlled in rate by a frequency-beat oscillator. In a few cases a Harvard inductorium was used.

Results

A. *Stimulation of postganglionic fibers.* As explained under Method it was sometimes difficult to include all the short ciliary nerves in the electrodes. As a consequence the contractions of the pupil were not always uniform (Fig. 1 and 2).

In 12 animals series of brief periods of stimulation at different frequencies were recorded. Figure 1 illustrates typical results. It is interesting that the maximal construction was obtained at about 25 per sec., a frequency similar to those which yield maximal responses in other autonomic neuro-effector systems (see Rosenblueth, 1932).

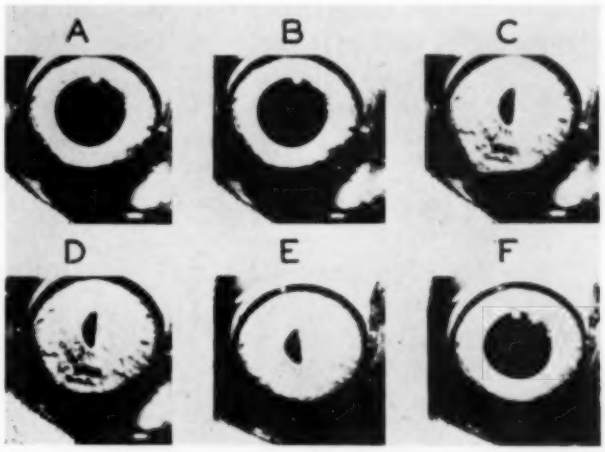

FIG. 2. Prolonged stimulation of the postganglionic parasympathetic supply to the iris at the frequency of 60 per sec. Superior cervical ganglion removed 12 days previously.

A and B: 2 and 0.5 min. before stimulation. C to E: 0.5, 2, and 120 min. after the beginning of stimulation. F, 1 min. after the end of stimulation.

For the study of the 4th and 5th stages the frequencies of stimulation used were 50 to 130 per sec. In 12 of the 20 experiments performed the frequency was 60 per sec., since Rosenblueth and Luco (1939) and Lanari and Rosenblueth (1939) found that this rate of stimulation was optimal for the separation of those stages.

Continuous maximal stimulation of the postganglionic parasympathetic fibers at the frequencies mentioned caused contractions of the sphincter muscle of the iris, which were maintained for 1 to 2 hours, as shown in Fig. 2. If the stimulation was prolonged further there was a gradual decrease of the response, but in no instance was there a late increase corresponding to a 5th stage.

In two experiments the postganglionic sympathetic fibers to the iris were stimulated for 1 hour at a frequency of 60 per sec. The results confirmed the report of Lanari and Rosenblueth (1939), *i.e.*, there was a dilatation of the pupil throughout the period of stimulation.

The responses to stimulation of either the sympathetic or the parasympathetic postganglionic supply to the iris are therefore similar. The contraction of the responding muscle is sustained for a long time. There is only a late and slight fatigue. There is no evidence of a late recovery (5th stage) following this fatigue (4th stage).

B. *Stimulation of preganglionic fibers.* Thirteen experiments were performed, with prolonged stimulation at frequencies of 25 to 150 per sec. With frequencies of 25 or 30 per sec. no fatigue was seen after a 90-min. stimulation. With frequencies of 60 to 150 per sec., typical 4th (Fig. 3C to F) followed by 5th stages (Fig. 3H to M) were recorded.

If, after the 5th stage had developed, the muscle was allowed to rest for

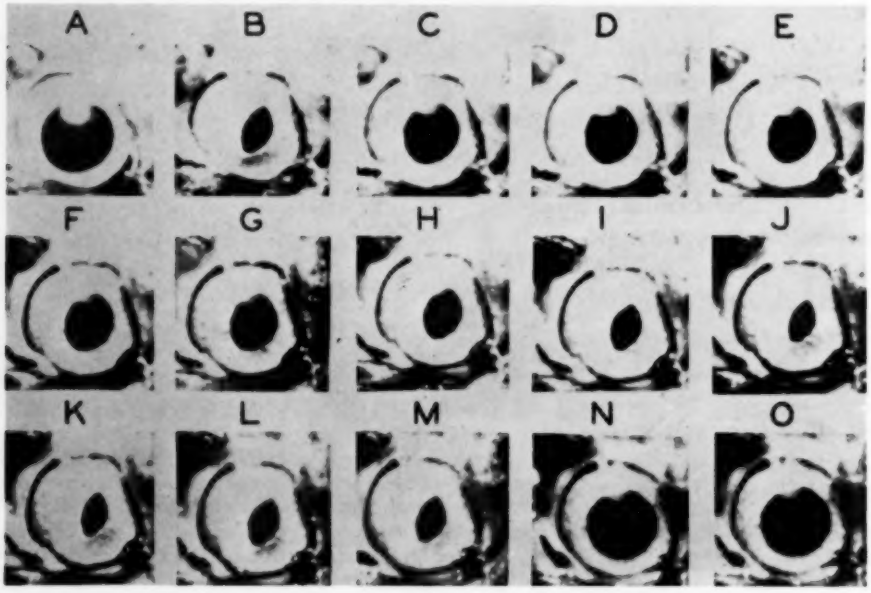

FIG. 3. Prolonged stimulation of the preganglionic parasympathetic fibers in the IIId cranial nerve at the frequency of 100 per sec. Adrenal glands ligated.

A: 2 min. before stimulation. B: 5 sec. after the beginning of stimulation. C to M: 2, 5, 15, 20, 26, 33, 40, 50, 64, 95 and 100 min. after the beginning of stimulation. N and O: 1 and 4 min. after the end of stimulation.

20 to 30 min., reapplication of the stimuli again ensued in a 4th and then in a 5th stage.

The results of stimulation of the parasympathetic preganglionic fibers to the iris are therefore similar to those found by Lanari and Rosenblueth (1939) in the preganglionic supply to the heart (parasympathetic) and to the nictitating membrane and iris (sympathetic).

DISCUSSION

That the parasympathetic component of the short ciliary nerves is cholinergic in the rabbit was shown by Engelhart (1931). In cats, similar results were obtained by Luco and Lissák (1938), *i.e.*, stimulation of these parasympathetic nerves releases acetylcholine in the aqueous humor of the eye.

During stimulation of the cholinergic postganglionic parasympathetic

fibers the typical results seen in other cholinergic fibers were not obtained (cf. Fig. 2 and 3). The results of that stimulation were similar to those obtained with adrenergic postganglionic fibers. It may be concluded, therefore, that the ability to elicit a late rise of response (5th stage) after an initial fall (4th stage) is not a general property of cholinergic nerve fibers, but only of preganglionic and motor axons.

Rosenblueth, Lissák and Lanari (1939) have shown that the five stages of ganglionic or neuromuscular transmission may be explained by changes in the output of acetylcholine from the presynaptic nerve endings. If this explanation is accepted, it should be assumed that the output of acetylcholine from postganglionic parasympathetic fibers does not undergo the changes which take place in preganglionic or in motor nerve fibers. The output of acetylcholine in postganglionic elements declines slowly during a prolonged stimulation. Similarly, the release of adrenaline from adrenergic fibers probably decreases only slightly over prolonged periods of stimulation.

Summary

The optimum frequency for brief periods of stimulation of the parasympathetic nerve supply to the cat's iris is 25 per sec. (Fig. 1).

Prolonged stimulation of the postganglionic parasympathetic fibers at frequencies of 50 to 150 per sec. results in a contraction of the sphincter of the iris which is sustained for 1 to 2 hours and which thereafter gradually declines (Fig. 2). There is no evidence of a 4th stage followed by a 5th stage of increased contraction.

Similar prolonged stimulation of the preganglionic fibers in the IId cranial nerve results in a marked contraction followed by a fall (4th stage) and later by an increase of response (5th stage).

It is concluded that the appearance of the 5th stage is not a property of all cholinergic nerves, but only of preganglionic and motor fibers.

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ISOLATION OF RETINAL AND OPTIC GANGLION RESPONSE IN THE EYE OF *DYTISCUS*

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INTRODUCTION

IT HAS long been recognized that the electroretinogram of the vertebrate eye in the standard leads "cornea-back of the bulb" consists of several component potentials. Algebraical summation of such potentials has been held to account for the polyphasic response to illumination (Kuehne and Steiner, 1880; Einthoven and Jolly, 1908; Piper, 1911; Kohlrausch, 1918). The presence of three such components, PI, PII, PIII has been established by the experiments of Granit and his collaborators (see summary by Granit, 1938).

One of the difficulties with the vertebrate eye is that localization of the components has to be carried out on an eye in which the receptors are directly joined to two ganglionic layers. For this reason it is of importance to carry out some analytical work with other types of eyes in which different layers of the visual apparatus are anatomically separated or separable. In the eye of the water-beetle I have found it possible to separate the visual cells from the optic ganglion and also to demonstrate how electrotonic spread may complicate evaluation of a complex potential made up of the primary visual response and the electrical phenomena in the ganglion. The outcome of this work will be reported below.

Actually, the eye of *Dytiscus* has been studied previously by Adrian (1936) who did not attempt to discriminate between potentials from different sources but chiefly devoted himself to describing various types of rhythmic activity recorded from the optic ganglion. Hartline in 1925 gave a brief description of electroretinograms from different insect eyes without attempting to analyze them. Later Jahn and Crescitelli (1938, 1939; see also Crescitelli and Jahn; 1939a, b), have recorded the complex response to light of a number of insects. Probably the simplest visual response hitherto recorded is that of the arthropod *Limulus polyphemus* (Hartline, 1925; Hartline and Graham, 1932) which is wholly due to the receptors. Recent work by Therman (1940) indicates that even a single stratum of visual cells in the eye of cephalopods may react to light in a relatively complex manner (*cf.* old work by Beck, 1899; Piper, 1904; Fröhlich, 1914). The comparison with the results of other workers will be found in the discussion.

COMPOUND EYE AND OPTIC GANGLION OF *DYTISCUS*

The compound eye of the water-beetle occupies a large part of the lateral wall of its head and, according to Leinemann (1904), consists of 9.000 ommatidia placed fan-like. To each ommatidium belongs a cornea-lens and the sexangular cornea facettes form a highly convex surface. The distal curvature of each lens (cl in Fig. 1) is insignificant but the proximal surface is highly curved so that the compound cornea is of considerable thickness.

According to the work of Guenther (1912) the *ommatidium* (Fig. 1) is built in the following manner: Just inside the *lens* there are 4 Semper's cells (kkzk) surrounding a conical *crystal interior* part (kk). These form a cover around the crystal cone reaching to the distal parts of the outer retinula cells (kks). The *retinula cells* (rt) are a drawn-out cell. group with a distal swelling in the region of the nuclei of the outer cells (rtzk) and a proximal enlargening caused by the nuclei of the basal retinula cells (bz). In the prototype ommatidium there are 7 radially placed retinula cells around an eighth central cell. This type of ommatidium with 8 visual cells seems to be present in the majority of insects and should be regarded as the original form (Plate, 1924). But in the water-beetle (Guenther, (1912) as well as in many other beetles (Plate, 1924) the central cell descends down towards the basal membrane to form the so-called basal cell (bz). Of the remaining radially placed cells one is expelled in the proximal zone and therefore does not take part in the formation of the rhabdome.

The *rhabdome* (rh) is a rod-like homogeneous structure surrounded by the retinula cells and placed in the centre of the ommatidium. It consists of a highly refractive substance, probably formed by the inner surfaces of the six radial cells and the basal cell. From the rhabdome excitation is held to be transmitted to the retinula cells (visual cells).

From the latter and the basal cell the nerve *fibres* arise (nf), and penetrate the basal membrane soon to end in the optic ganglion. According to Guenther they pass a layer of nerve cells just under the basal membrane. According to Holste (1923) this layer would merely be a dendritic branching of the fibres. Between them would be supporting cells and pigment cells.

The optic *lobe* is a 1.5 mm. long pear-shaped structure with its basis towards the compound eye and the apex tailing off into an optic nerve. Its organization is very complex. The general plan seems to be that the nerve cells are found in an outer layer surrounding a central nucleus of interconnected dendrites (for details, see Holste, 1923). From the optic lobe the optic nerve runs to the supra-oesophageal ganglion (sg Fig. 2). The distance from the layer of retinula cells to this ganglion is about 2.5 mm.

In the eye of *Dytiscus* the dioptric apparatus of each ommatidium is at some distance from the rhabdome (see Fig. 1). At moderate intensities the various ommatidia are optically badly isolated on account of the lack of pigment between them. In this state the eye of *Dytiscus* should be regarded as a *superposition eye*. This means that rays from the object reach the same rhabdome through several facettes there to add their excitatory effects. Intense illumination, however, leads to movement of the pigment in between the ommatidia. This favors optical isolation. Thus a smaller number of rays from a given object are projected onto each rhabdome. The decreased summation leads to decreased sensitivity and the eye changes into an *apposition eye* (Plate, 1924).

The pigment cells (ip) bringing about this change are partly found distally round the crystal cone, and partly at the basis of the retinula cells. Intense illumination makes the pigment of the outer layer move inwards towards the basal membrane, whereas the inner pigment moves towards the cornea. Below a certain strength of illumination follows withdrawal of the pigment.

FIG. 1. Section along three ommatidia in the eye of the water-beetle. Explanation in text (after Guenther, *Z. wiss. Zool.*, 1912, *100:* 60–115).

TECHNIQUE AND PROCEDURE

Apparatus. Recording of the action potentials was carried out with a cathode ray oscillograph in conjunction with a three-stage push-pull directly coupled amplifier, designed by the physicist of this laboratory, Mr. T. Helme. Absence of drift has been systematically controlled. Time was recorded in 0.2 and 0.4 sec. with a Rayleigh-wheel. As stimulus served "white light" from a hundred watt bulb; Wratten neutral tint filters of standardized intensity were used for variations of intensity.

Preparation. (Cf. Adrian, 1937.) The wall of the isolated head was lifted up and the underlying strong muscles removed until the supra-oesophageal ganglion and the optic ganglion were layed bare. These ganglions were freed from adjoining tissue, and the supra-oesophageal ganglion was lifted up to rest upon an electrode (5 in Fig. 2) taking care to keep the optic nerve between them intact. In this manner the optic nerve and the optic ganglion were isolated by air up to the basal membrane, and the other electrode could be given different positions on the optic pathway. In order to lead off from the front of the facette eye a small hole was cut in the chitinous cornea through which the fine point of the electrode could be inserted. Owing to thickness of the lens this could be done without damaging the visual cells.

As electrodes were used silver-chloride pins covered with cotton wicks drawn out into a thin point. Now and then the preparation was irrigated with Ringer solution. Leads could also be taken from the isolated compound eye after cautious removal of the optic ganglion (leads 1–2). In such cases histological control showed that the point of severance was in the region of the basal membrane.

When dark-adapted animals were used these had been in the dark for 12 hours. As pointed out by Adrian (1937) the optic nerve may keep alive for 3–4 hours and the ganglion for a very much longer time if prohibited from drying. In quantitative work 2 hours has been the limit in these experiments and the repeated response to a standard intensity has been used as a check upon the state of the preparation.

Results

Intact preparation. Record a of Fig. 3 shows the typical effect from the optic ganglion (leads 3–5 of Fig. 2) of a fresh preparation and is in essential agreement with pictures given by Adrian (1937). As pointed out by him the electrode (5) on the supra-oesophageal ganglion can be regarded as a reference electrode. This is shown, for instance, by the fact that crushing this ganglion does not alter the potential change. The baseline before the onset of light in Fig. 3 shows that there was no definite resting activity. Illumination leads to a strong sustained negativity under the electrode of the optic ganglion relative to the proximal electrode. (In this as in all other records an upward deflection marks negativity of the distal electrode relative to the proximal one.) The negativity of the ganglion first rises rapidly, then more slowly to a plateau. If illumination be continued for a longer time the potential very slowly diminishes (cf. Fig. 4a and 5a). On the slow potential (Fig. 3a) there are superimposed irregular oscillations, some of the nature of spikes, others slower changes. These stop abruptly at cessation of illumination and after an upward peak the negativity diminishes. This rather complicated picture recurs with great regularity when the active electrode is placed on the proximal part of the pear-shaped optic ganglion.

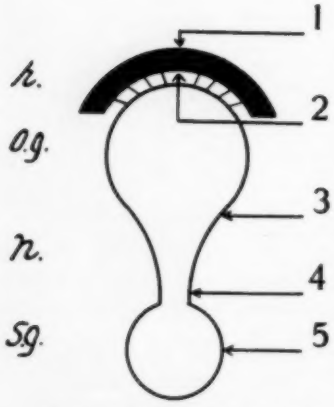

FIG. 2. Schematic drawing of an eye prepared for an experiment with receptorial layer (r), optic ganglion (og), optic nerve (n), and supra-oesophageal ganglion (sg). The numbers 1–4 show the different loci used for the active electrode, whereas 5 is the constant locus of the reference electrode on the supra-oesophageal ganglion.

Some of the typical "later reactions" (Adrian) of this preparations are

illustrated by Fig. 3b, c and d. After an hour, and sooner if the preparation is damaged or drying, the irregular oscillations of low amplitude, caused by strong illumination, tend to fall into a well developed regular thythm at 10–20 beats per sec. This "bright rhythm" follows upon illumination (see Fig. 3b and 4b) and disappears when the light is cut off. On the other hand, if the preparation be left in the dark there arises a rhythmic discharge ("dark rhythm") with a frequency of 6–8 per sec. (Fig. 3d), which disappears upon illumination to be replaced by the "bright rhythm." When the light is turned out the "dark rhythm" returns progressively, as illustrated by Fig. 3c. Adrian came to the conclusion that these rhythms were to be regarded

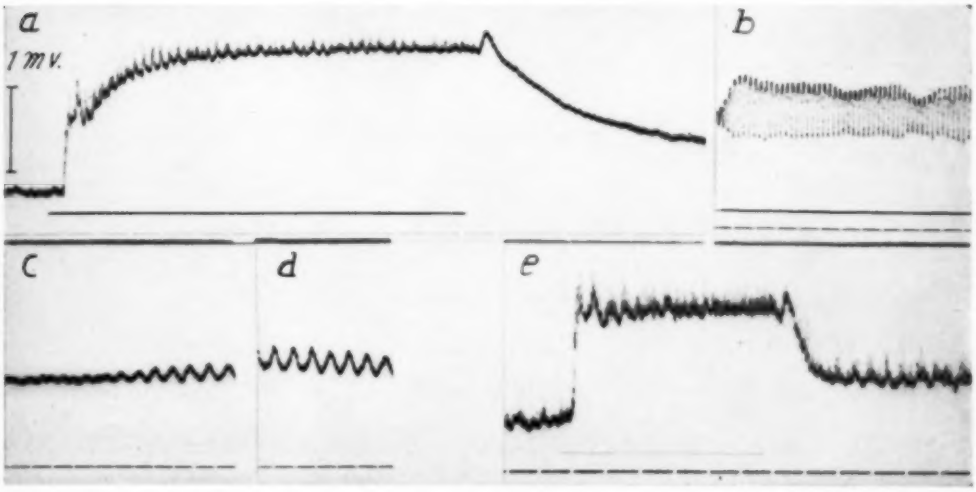

FIG. 3. a, potential activity of the optic ganglion (leads 3–5) following illumination of the eye. b, "bright rhythm." c, beginning of the "dark rhythm." d, "dark rhythm" fully developed. e, as in a, but with spontaneous activity present. Time in $\frac{1}{2}$ sec.

as the result of synchronized activity in a large number of units. Strong illumination or darkness seemed to be the main conditions for the appearance of synchronized beats. In the former case the rhythm was held to reproduce the maximal frequency of the neurons, in the latter their natural resting discharge.

Figure 3e shows a special phenomenon visible also in records 5a and b. In this case the ganglion has begun by discharging spontaneously, chiefly rapid spikes, in the dark. Upon illumination there is added to these the fast potentials caused by the light. At cessation of illumination the latter disappear, as in Fig. 3a, at the same time as the upward "off-deflection" appears. But, whereas in Fig. 3a the baseline after cessation of illumination is quiet, just as it was before the eye was illuminated, in Fig. 3e there recurs on the falling phase of negativity the spontaneous activity noted already in the dark. The interesting point here is that the spontaneous activity is inhibited during the "off-deflection" itself, the latter being almost free from spikes.

The farther up on the optic nerve the active electrode is placed the smaller the negativity caused by illumination. Records a and b in Fig. 4, with the active electrode placed between 3 and 4 (Fig. 2) have been taken with a faster film. Here spike activity is better visible on the slow potential. There is a heavy initial discharge slowly falling to a constant frequency kept up as long as illumination sustains the negative potential (cf. Fig. 13). Similar leads have been used for record 5a and b after development of the

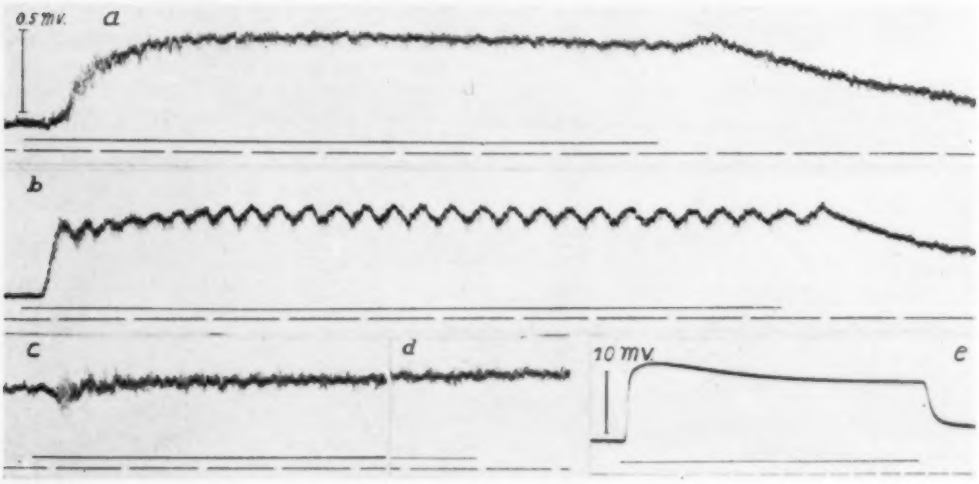

FIG. 4. a and b, action potentials from the optic ganglion in the fresh (a) and ageing (b) preparation. Active electrode between 3 and 4. c and d, spike potentials from the optic nerve (leads 4–5) at "on" (c) and "off" (d). e, potential of isolated compound eye (leads 1–2). Time in $\frac{1}{5}$ sec.

regular "bright rhythm." In this figure should be noted the rhythmic grouping of the rapid spike potentials. In parallel with the development of the slow beats at 12 per sec. the spike potentials are found to be grouped chiefly on the rising phase of the potential wavelets. As long as these are absent, as in record 4a, the spike potentials are relatively evenly distributed (cf. Adrian, 1937).

In leads 4–5 on the nerve in the vicinity of the s.o.-gangilon (Fig. 4c) there is no slow potential whatever but only spike potentials in the nerve arranged in groups corresponding to the rhythm of record 4b. The downward swing of these spike potentials in records 4a and b suggests that in this case they come from the proximal electrode. Such pictures are sometimes obtained and signify that the electrode on the s.o.-ganglion is placed near the point of entrance of the optic nerve. The off-deflection is clearly visible in records 4a and b and these as well as Fig. 4d demonstrate the abrupt cessation of spike potentials when the light is turned off.

This series of pictures thus shows how the typical effect, as led off from the optic ganglion, consists of a slow negativity which diminishes in ampli-

tude when the active lead wanders towards the s.o.-ganglion. Cessation of illumination is followed by a definite off-deflection accompanied by inhibition of spike activity. Rhythmic waves may occur on the slow negativity and their frequency after illumination seems to coincide with the frequency of the grouped impulses in the nerve.

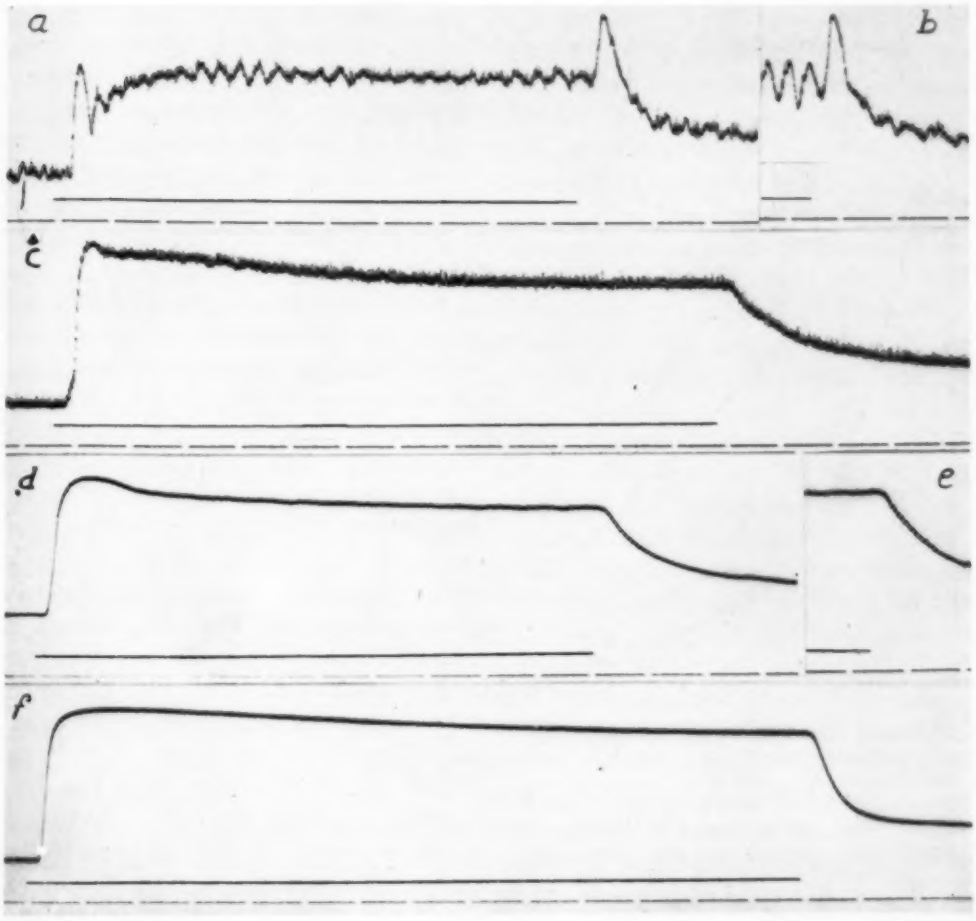

FIG. 5. Cocaine experiments, a and g, normal optic ganglion potential (leads 3–5). c, some minutes after 4 per cent cocaine. d and e, later after cocaine. e, potential of isolated compound eye control (leads 1–2). Time in $\frac{1}{5}$ sec.

If the optic ganglion and the central parts of the visual path be severed from the compound eye in the region of the basal membrane and leads 1–2 be used, illumination still elicits a large slow potential of upwards 10–15 mV as shown by Fig. 4e. This record is from a moderately dark-adapted eye. The electrode in the front, without exception, is negative relative to the electrode on the back of the eye. In this case the negativity directly rises to

its maximum, and after a drawn-out top passes over into a slightly sloping plateau (cf. Fig. 9a). When the light is turned out the negativity first drops quickly to a certain level from which follows a very slow descent towards the baseline. This is best seen in slow films, as Fig. 9a. The isolated compound eye (*i.e.* the retina *minus* optic ganglion) always gives a monophasic effect. There are never any superimposed potential waves nor negative off-deflections.

This circumstance that the isolated compound eye only gives a strong negative potential upon illumination suggested that the sustained negativity, led off from the optic ganglion, in reality belongs to the eye itself. Experiments with cocainized ganglions, as we shall see, support this conclusion.

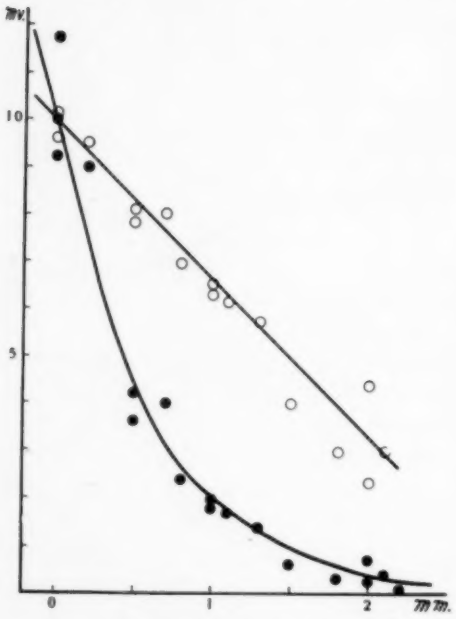

FIG. 6. Decrement of the retinal action potential along the visual path plotted in terms of size of response against distance in mm. from the receptors (filled circles). The log of these values (open circles) also plotted against the same abscissa. Zero on the abscissa represents the potential as led off directly from the compound eye itself.

Ganglionic action potential after cocainization. In record a in Fig. 5 there is first the characteristic response from the optic ganglion (leads 2–5) already described. There is definite spontaneous activity in the dark and a tendency to rhythmic waves before and after illumination. After the initial rise of the potential there is a definite swing-back before the effect slowly rises towards its maximum (cf. Fig. 3a). When a drop of a 4 per cent cocain solution has been applied to the ganglion the type of the response totally changes (Fig. 5c). The electrodes have not been moved. The initial swingback has disappeared, and so have the rhythmic potential waves as well as the off-deflection. There remains only the large negative potential upon which is superimposed an even flow of impulses in which transition from spontaneous activity to stimulated activity cannot be discerned. At a later stage spike activity also disappears and the negative potential of Fig. 5d tends to assume the shape of the isolated retinal action potential from the compound eye alone (Fig. 5f, leads 1–2). Even an increase of the type of exposure (Fig. 5e) cannot provoke an off-deflection (cf. Fig. 5b).

This and other similar experiments demonstrate that the effect, as recorded from the optic ganglion, partly consists of a strong sustained negativity almost certainly emanating from the receptors, and partly of effects

from ganglion and nerve fibres superimposed upon the latter. The optic ganglion contributes an effect both at "on" and "off" in addition to potential waves during illumination. These effects sum algebraically with the potentials from the retina. The relation between the retinal action potential and the ganglionic effect will be discussed below.

Decremental spread of the retinal response along the optic pathway. The experiments with cocain made it highly probable that the response remaining after cocaine is nothing but the retinal response picked up from the ganglion. Seeing how in Fig. 4 the amplitude of the sustained negative response diminishes, the further the leads are from the receptorial layer, it became necessary to investigate this factor systematically with our standard illumination and electrode 5 on the s.o.-ganglion as reference point.

Four such experiments have been averaged in the diagram of Fig. 6 to show the amplitude of the response (filled circles) against distance of the active electrode from the receptorial layer. Zero on the abscissa means that the leads are taken from the compound eye itself (1–5 in Fig. 2). Size of the visual response falls along the optic pathway in an exponential manner, as shown by the straight line obtained when log amplitude is plotted against distance (open circles in Fig. 6).

The spatial decrement of the slow negativity in the diagram suggests electrotonic spread. The decrement follows the equation $P_p = P_r \cdot e^{-ax}$ in which P_p represents the maximal amplitude at the postretinal electrode at distance $\times$ cm. from the receptorial layer and P_r is the maximal amplitude below the receptor electrode (cf. Bogue and Rosenberg, 1934 for polarization of peripheral nerve and Eccles, 1935 for the post-ganglionic trunk in the superior cervical ganglion). The electrotonic constant a in this case is about 16, indicating relatively limited spread of the retinal action potential.

A polarizing current of sub-threshold strength and rectangular shape gives in the sciatic nerve of frog at zero distance an electrotonic potential with approximately exponential rise (Bogue and Rosenberg, 1934). With increased distance of active electrode from the polarizing circuit the electrotonic potential has an S-shaped rise and a lower and somewhat later maximum. Similar changes with increased distance from the point of origin also characterize the sustained negativity of the eye of the water-beetle. Thus, record 4a which has been taken at a distance of about 1.5 mm. from the eye illustrates the slow creep from the baseline and S-shaped rise of the response. Even when taken directly from the compound eye the potential does not leave the baseline instantaneously, although it rises far more rapidly and sooner reaches its maximum compared with the preceding case (visible, for instance, in Fig. 4a compared with 5f despite different speed of the film).

The slow rise of the potential makes it difficult to locate its earliest point. Another complication is the on-effect from the ganglion, mentioned above (see Fig. 3a and 5a), which falls into different regions of the rising phase dependent upon the locus of the active electrode. But taken as a whole these experiments on electrotonic spread support the conclusion that the

main part of the sustained response is nothing but the retinal action potential which has spread electrotonically to the ganglion.

The potential of the compound eye. One may ask whether the monophasic, relatively simple retinal action potential is homogeneous or whether it consists of components with different function or significance. From this point of view the striking difference between its rising initial phase and its descent to the baseline is of particular interest. Apparently illumination leads to a depolarization of the receptorial layer causing its proximal end to be negative relative to the neurones.

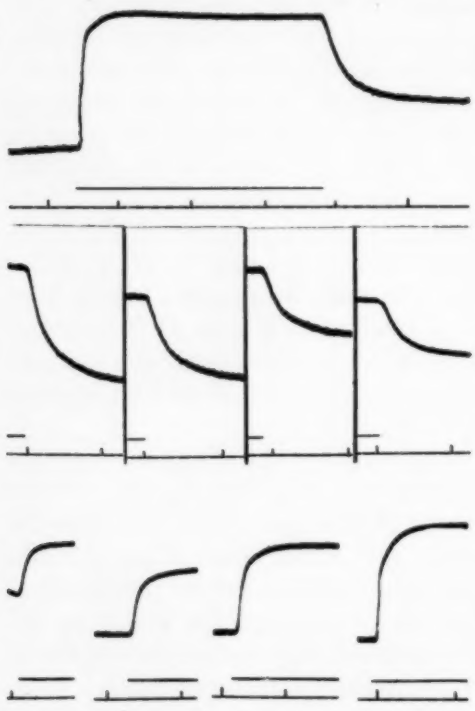

FIG. 7. Potentials of isolated compound eye (leads 1–2). Upper record, control. In the middle row off-effects after respectively 0.5, 1, 15, and 30 sec. illumination. Lower records illustrate "on"-effects for intervals 0.5, 4, 15, and 30 sec. after cessation of previous illumination. Time in $\frac{1}{5}$ and 1/1 sec.

In Fig. 4a and 5f, and particularly after the long exposure in Fig. 9a, one can distinguish two phases with different temporal properties in the fall of the curve after cessation of illumination. There is an initial rapid drop, varying in extent from case to case, and falling to a level from which the potential then slowly diminishes. The first rapid phase is complete within about 0.2 sec. But it lasts some 30–60 sec. before the potential has reached zero from this level. These changes are clearly dependent upon time of exposure.

A. Different times of exposure. Records in the middle row of Fig. 7 show the fall of the retinal action potential of the isolated compound eye for different times of exposure (0.5–30 sec.). Between each exposure there has been an interval of rest of more than 1 min. and the maximal amplitude of the negativity has been checked up and found to be constant and of the order of magnitude of the initial deflection in the upper record of Fig. 7. After an exposure of 0.5 sec. the retinal response drops rapidly about 85 per cent of its initial value to be followed by the slowly diminishing remainder. But after an exposure of 30 sec. the fast drop of the response is only about 40 per cent of its initial rise. At the same time it tends to tail off more slowly into the later phase. An experiment of this type is shown schematically in Fig. 8, where the course of the fall of the response towards the baseline for different exposures is put in along the sustained negativity and the values are given in per cent of the maximal ampli-

tude of the negativity. The dotted curve shows the level reached by the rapidly falling phase at different exposures.

As already pointed out the initial rapid drop lasts about 0.2 sec, but it takes up to a minute before the potential almost rectilinearly reaches zero. If after a previous exposure the stimulus is reintroduced, the light causes reappearance of the visual response which then reaches an amount of potential which roughly corresponds to the level attained by the preceding retinal action potential. And the new effect rises from that particular point

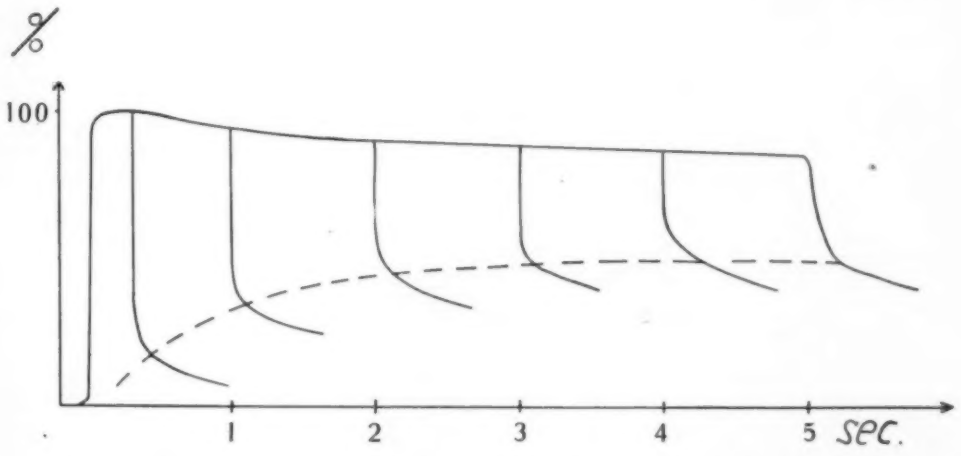

FIG. 8. Diagram showing the course of fall of the retinal negativity towards the base-line after varying times of exposure. The dotted line shows the level to which the rapidly falling phase of the vanishing response drops at "off." The values are in per cent of the maximal amplitude of the retinal response.

on the slowly falling phase of the preceding stimulus which corresponds to the interval between cessation of the one and initiation of the other response. Thus, on account of the fall in the level of the potential, as it slowly declines in the dark, the amplitude of the reintroduced visual response will increase when this interval of darkness increases. A series of such responses recurring after different intervals is shown in the lowermost record of Fig. 7 to be compared with the uppermost curve of the same figure taken after a dark interval of more than a minute.

The upper record of Fig. 9 shows the sustained visual response of the isolated compound eye after an exposure of 90 sec. The potential slowly falls during the first 30 sec. thereafter to remain at a practically constant height. The lower record shows the effect of a very slow flicker at 1–2 per sec. With this intermittent stimulus the upper contour is a copy of the effect of continuous illumination. The lower contour marks approximately the level of the rapid drop, as with this rate of stimulation the slow fall has not time to appear before the next flash of the intermittent stimulus sets in. Compared with the experiment, shown in Fig. 8, the level to which the rapid drop of

potential falls, sooner reaches its maximal value which also is greater than in Fig. 8. The determinants for these variations will be discussed below.

B. Different intensities. In the experiments illustrated in Fig. 10 a long exposure of 20 sec. has been chosen so that the rapid fall at "off" is small

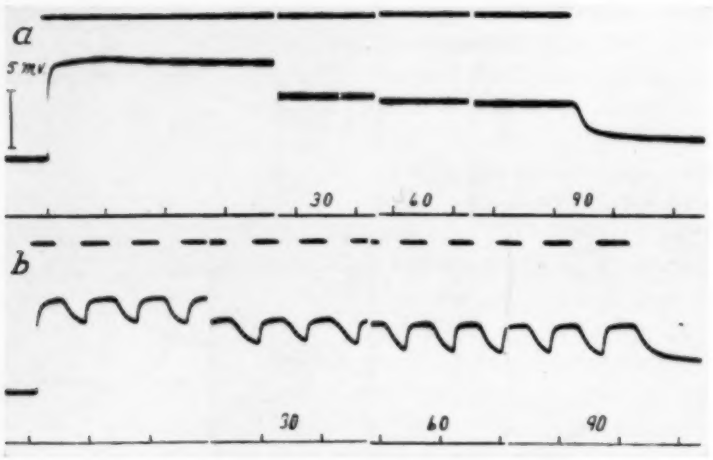

FIG. 9. Response of isolated compound eye to 90 sec. of continuous (a) and intermittent (b) illumination. Time in sec.

(cf. Fig. 8) at the highest intensity (intensity 1 in Fig. 10a). The initial drop at "off" is only about 10 per cent of the maximal amplitude of the response.

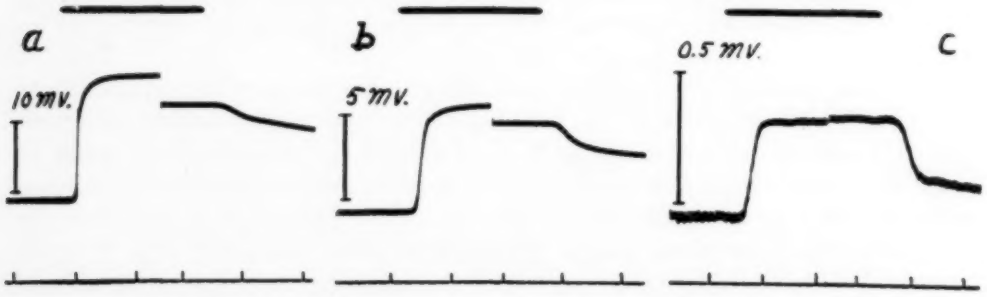

FIG. 10. Response of isolated compound eye to 20 sec. illumination with intensities 1 (a), 1/100 (b) and 1/10,000 (c). Time in sec.

When illumination was diminished to 1/100 the total retinal action potential decreased to less than half, whereas the initial drop at "off" was 20 per cent and thus in absolute terms was practically unaltered. Finally, at the intensity 1/10,000 the retinal response was reduced to 1/50 and now the rapid fall practically reached the baseline. The average result of 5 such experiments is shown graphically in Fig. 11. In all experiments time of exposure has been 20 sec. and 5 intensities have been tested. Both the values for the

total amplitude of the retinal action potential (filled circles) and the rapid drop at "off" (open circles) are plotted in per cent of the maximal response against log intensity. The diagram shows how the retinal action potential

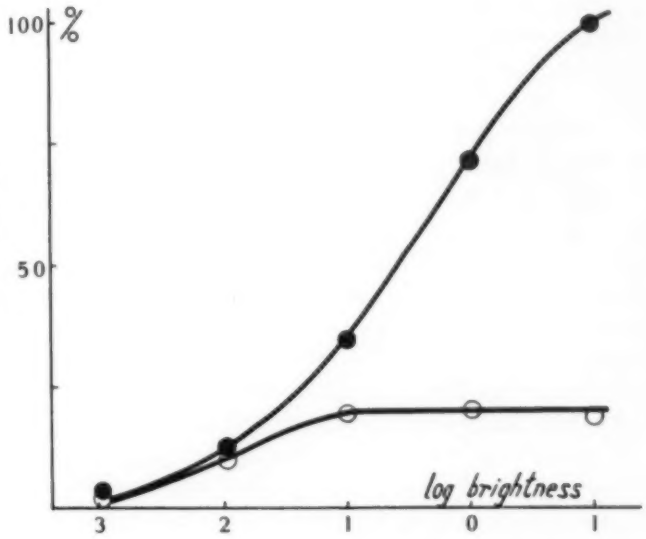

FIG. 11. Plot of the amplitude of the total response (filled circles) and of the rapid drop at "off" (open circles) against log brightness. Values in per cent of total response to maximal intensity (intensity 1).

rises as the intensity increases. The amplitude of the rapid drop at "off," however, follows quite a different course. It is clear that, as long as the curves run together, this also means that the whole visual response disappears with the rapid drop at "off." This is seen to be the case at the lowest intensities (1/10,000, 1/1000). But at the higher intensities from 1/100 upwards the rapid drop of potential at "off" asymptotically reaches a maximum although the total visual response now increases very rapidly. In proportion to the latter the fall therefore looks smaller and smaller. Thus, at higher intensities, an increasingly greater part of the total fall of potential at "off" will consist of the slowly falling phase. The rapid depolarization at "on" and the rapid repolarization at "off" behave very differently at different intensities.

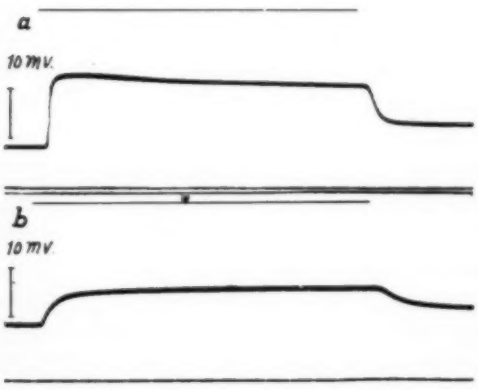

FIG. 12. Response of dark-adapted (a) and light-adapted (b) isolated compound eye. Time in $\frac{1}{5}$ sec.

Figure 12 shows the difference between the retinal action potentials of light- and dark-adapted water-beetles. After prolonged dark-adaptation

the visual response rapidly reaches large values and also disappears rapidly when the light is turned off. But if the eye is left illuminated for 8–10 min. and then, after 1 min. in the dark, is stimulated with the standard intensity (lower record in Fig. 11) the visual response looks quite different. Its rising phase is slower and amplitude lower and at cessation of illumination it also disappears along a drawn-out curve.

Discussion

Adrian (1937) held the large potential recorded from the optic ganglion of the water-beetle including the rhythmic beats in darkness and those elicited by bright light to be due to the optic ganglion itself. But we have seen now that the retina of the isolated compound eye lacking its ganglion cells reacts to light with a large sustained negativity spreading electrotonically along the optic path down to the ganglion from which it also can be recorded. Even if Guenther's view that there is a separate layer of cells just below the basal membrane be correct, these cells can hardly be responsible for this very large potential, the less so as histological controls have shown that in some of the experiments with isolated eyes even the basal membrane has been torn away. Illumination clearly leads to a depolarization of the receptors themselves making their distal end negative in relation to the back of the eye including the post-receptorial fibres.

The eye of cephalopods (Beck, 1899; Piper, 1904; Fröhlich, 1913) which also consists of receptors alone gives a similar monophasic negative potential. Among arthropods the lateral eye of the horse-shoe crab (*Limulus polyphemus*) is known to react in the same manner (Hartline, 1928; Hartline and Graham, 1932). The eyes of other arthropods (*Melanoplus chortophaga, Vanessa, Musca, Bombus*) according to Hartline (1928) may show a diphasic variation of the chief negative potential. Later work with insects (*Melanoplus samea*) has shown that sometimes a positive initial deflection may precede the prolonged negative receptor potential (Crescitelli and Jahn, 1939a, b; Jahn and Crescitelli, 1938–39). But these experiments have been carried out on eyes *in situ*. Under such circumstances complex responses may be obtained also from the retina of *Dytiscus*, which when properly isolated always respond with a simple monophasic potential.

It is obvious that polyphasic responses may be caused by currents spreading over inactive tissue to the second electrode which cannot be regarded as indifferent (cf. Gilson and Bishop, 1937; Eccles, 1939). Complex responses may also be caused by processes in the optic ganglion as shown above. Thus, for instance, Hartline's picture from *Vanessa* looks like the combined response of retina and optic ganglion in *Dytiscus* (leads 1–5).

These considerations do not exclude the possibility that in the receptors of some insects there may be processes of opposite potential sign. They merely serve to emphasize that such phenomena have not yet been convincingly demonstrated. Actually Therman (1940) has found two processes of opposite potential sign in the isolated eye of the cephalopod *Loligo*, re-

acting somewhat differently to different agents. Whether similar phenomena can be shown to occur in the eye of the water-beetle remains to be investigated. So far they have not turned up.

On the other hand it will be necessary to deal with two monophasic potentials of identical sign in *Dytiscus*, as shown by the experiments of Fig. 7, 8, 10 and 11, analyzed above. The response of the *isolated* compound eye to relatively strong light is shown split into its two components in Fig. 13. The dotted line S of Fig. 13a represents the level to which the total

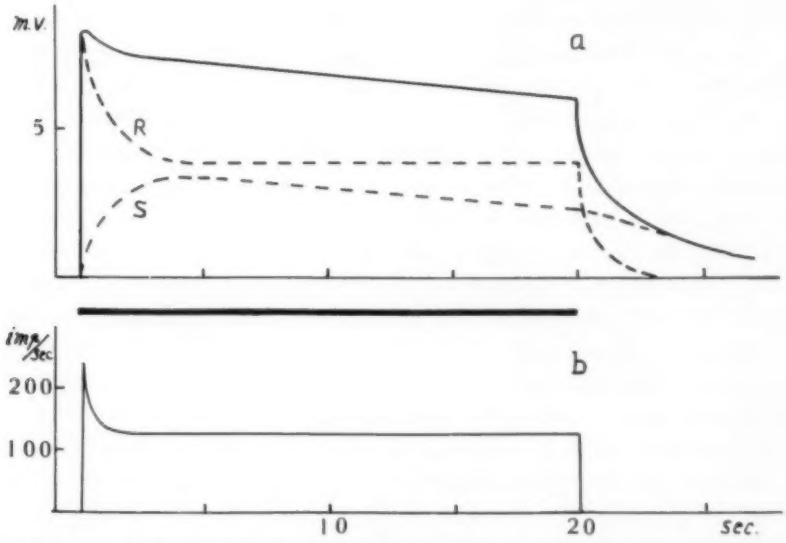

FIG. 13. a, analysis of the electroretinogram of the isolated compound eye (line drawn in full). Components drawn in broken lines, heavy black line indicates a stimulus of a duration of 20 sec. b, frequency of the impulses in the optic nerve plotted against duration of illumination.

potential falls upon cessation of illumination and is taken to illustrate the course of the slow component. It rises so slowly that at short exposures the total response has a large rapid drop at "off." After long exposures the drop at "off" decreases owing to the rise of S. As indicated in connection with Fig. 12 the latter component is largely responsible for the shape of the retinogram of the light-adapted eye. The difference between the total response and the superimposed slow component is given by curve R in Fig. 13a, illustrating a second fast component the peak of which probably is unduly accentuated. This component seems to be better marked in the dark-adapted eye and looks like an integrated frequency-time curve of the impulses in the optic nerve (see Fig. 13b). As shown by the experiments of Fig. 10 and 11 the maximal amplitude of the total response rises when the stimulus is being increased, whereas the fast phase of the repolarization at "off" rises only inside a relatively low range of intensities. At a certain level of intensity the initial deflection goes on increasing with further increases in

strength of illumination but the drop at "off" remains constant. This implies that the total response at low intensities chiefly consists of the fast component R whereas at higher intensities S becomes relatively more prominent. This explains why at low intensities (see Fig. 10c) the record shows an instantaneous drop at "off" and lacks the rounded top of the high intensity responses. There is further to be noted that at low intensities (Fig. 10c) the response remains at constant height whereas at height intensities it slowly decreases during illumination (see Fig. 10a and b). Unfortunately the peak of the component R cannot be obtained experimentally. This is because R predominates only at low intensities and because the peak probably is absent with weak stimuli, to be judged from the fact that the peak also is absent in the frequency-time curve of the impulses at such intensities.

Can we make any assumptions as to the nature of these components? Hanström (1937, 1938) distinguishes between two systems: Peripheral retinula cells with short nerve connections (*fibrae visuales breves*) to a first synapse, and basal retinula cells with relatively long nervous connections (*fibrae visuales longae*) to a more centrally placed layer of ganglions in the optic lobe. These suggestions have to be borne in mind as providing a possible explanation of the two component potentials in the isolated compound eye of *Dytiscus*, even though another explanation at the moment seems to be more probable. This is based on the fact that at higher intensities the retinal pigment moves up between the ommatidia. The slow course of the S-component is in favour of this view, as is also the fact that the impulses come and go much as the fast component R. In the dark-adapted state and at low intensities the pigment is contracted; it expands as the intensity rises and then again it slowly withdraws upon cessation of illumination. These properties do remind one of the properties of the slow component.

A comparison with the vertebrate retina suggests that the slow component might be identical with PI responsible for the c-wave (Granit, 1933–38; Granit and Riddell, 1934; Therman, 1938). The component PIII (Granit, 1933–38; Therman, 1938; Granit and Helme, 1939) is the one most likely to be the fast component R of the water-beetle's eye. But, taking into account the inversion of the vertebrate retina (Kuehne and Steiner, 1881), they are of opposite sign, and for this reason previous workers (Bruecke and Garten, 1907; Piper, 1911) have been inclined to identify the negative response of the cephalopod eye with the b-wave of the vertebrate retinogram which is part of its component PII (Granit, 1933). A possible solution of this discrepancy may be found in Terman's (1940) result that the receptor potential of *Loligo* has two components of opposite sign, both with properties reminiscent of the vertebrate component PIII. On this view PIII may turn up with different electrical sign, predominantly positive, predominantly negative, in different types of eye and under different experimental conditions.

Summary

Action potentials have been recorded from the isolated compound eye, the optic ganglion, and the optic nerve of the water-beetle (*Dytiscus marginalis*) with a directly coupled amplifier and a cathode-ray oscillograph.

The aim of the work has been to separate the activity of the isolated retina from the potentials in ganglion of nerve in order to study the properties of the former, all of which have been mixed in previous work with the same preparation.

The receptors in the isolated compound eye upon illumination react with a large monophasic potential, the front of the visual elements being negative relative to the back of the eye and postreceptorial fibres. No potential of opposite sign has ever been seen.

The properties of the retinal response have been studied in experiments with varying exposures and intervals of rest at constant intensity as well as for varying intensities at constant exposures. The experiments suggest that the monophasic response consists of two components of the same electrical sign: A slow one somehow connected with adaptation, and a fast one representing receptor activity. In the dark-adapted state and at low intensities the fast component predominates; in the light-adapted state and with strong stimuli the low component becomes visible.

The retinal response spreads to the optic ganglion with electrotonic decrement. The effect, led off from the optic ganglion, consists of the retinal response adding itself to specific potentials from the optic ganglion. There are in the latter deflections at both "on" and "off," and, under certain circumstances, rhythmic wavelets during illumination. The specific potentials in the ganglion disappears, when it is cocainized, so that finally only the monophasic response from the retina is left. The rise of the receptor potential coincides with an outburst of impulses in the optic nerve, soon falling to a constant frequency during illumination. When the light is turned off the impulses stop instantaneously and there is never any off-discharge to be seen.

During the off-deflection in the ganglion spontaneous activity in the nerve, if present, is inhibited.

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THE ACOUSTIC AREA OF THE MONKEY (*MACACA MULATTA*)

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THE TRANSVERSE temporal gyrus, Heschl's convolution, has traditionally been regarded as the site of termination of the acoustic thalamo-cortical radiations in man. Two principal lines of evidence may be adduced in support of this belief. Cytoarchitectonic and myelogenetic studies point to this area as one of characteristic histological structure (area 41 of Brodmann). Clinical studies, though meagre, tend to show that damage to the transverse temporal gyrus may result in hearing deficiencies.

In the monkey, there is usually on the superior (horizontal) surface of the superior temporal gyrus, near its broadened posterior extremity, a slight elevation which, it has been suggested, may be homologous with the human transverse temporal gyrus. Poliak (1932) states that the largest contingent of fibers of the acoustic radiation of the monkey terminates in the cortex of the elevation, although he also describes radiation fibers passing to all concealed surfaces of the superior temporal gyrus. Walker (1937), using the same species, found that a portion of the elevation is occupied by an area of koniocortex which he assumed to be primary acoustic projection area. Lesions involving this part of the superior temporal gyrus resulted in retrograde chromatolysis in the medial geniculate body.

The present study is an attempt to demonstrate by an electrical method the exact limits of the primary cortical acoustic projections, as has previously been done on the cat (Ades, 1941).

METHOD

In order to obtain adequate exposure of the superior temporal gyrus, it is necessary to remove the cortex and medullary substance of the inferior parietal and frontal lobes as illustrated in Fig. 1A. The entire hemisphere is exposed under deep nembutal anaesthesia and the areas mentioned are removed by means of a suction pipette so that the inferior lip of the lateral fissure as well as the insula is cleared, affording access for the electrode. The entire experiment is carried out under nembutal anaesthesia.

The stimulus consists of a sharp click generated by a thyratron relaxation-oscillator working through a power amplifier and delivered from a 10-in. speaker 2 ft. from the animal's head. The oscillator could be fired manually or by a timer. Recording of the stimulus was accomplished by means of a microphone placed close to the animal's head, and led through a transformer-coupled amplifier to the oscillograph.

Response from the cortex was recorded by leading from a unipolar silver electrode through a resistance-capacity coupled amplifier to a Dumont type 175A oscillograph.

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Simultaneous recording of stimulus and response on the same cathode-ray tube was accomplished by splitting the beam with a Dumont electronic switch.

Standard procedure was to move the electrode systematically in steps of approximately 2 mm. over the exposed inferior lip of the lateral fissure, recording the response from each point until the responsive area had been delimited. The responses shown in the figures were photographed from the single sweep (manually controlled) cathode-ray trace on 35 mm. Eastman 809 recording paper.

Results

Click stimulation produces an essentially diphasic response in the primary acoustic projection area of the monkey. The response is characterized by an initial large surface-positive spike, followed by a surface-negative phase, usually smaller in magnitude and longer in duration. Typical examples are shown in Fig. 2. It has essentially the same characteristics as the cortical response to appropriate stimulation in other afferent systems, as described by several previous authors. Some variability in the response is encountered. For example, at times the surface-positive phase seems to be the only component present. This is frequently due to the masking effect which the spontaneous potentials exert on the negative wave, as is shown by the fact that the negative component is nearly always perceptible when the base line is smooth. At times, the negative component is the larger or even the only visible portion of the response, a variation which may occur at any point within the boundaries of the area. This particular variation is unsystematic in its occurrence, and, from the results of the present study, can only be interpreted as due to temporary local conditions at the time recorded. The criterion for determining the boundaries of the acoustic projection area was, therefore, essentially

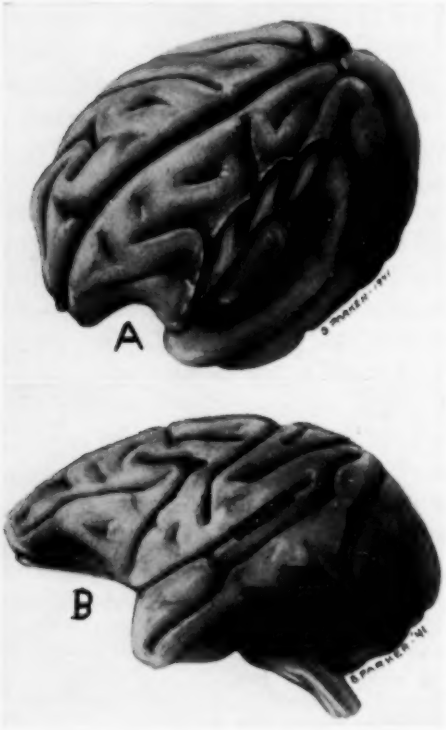

Fig. 1A. Fronto-lateral view of monkey brain showing exposure of superior temporal gyrus and insula.

Fig. 1B. Lateral view of monkey brain; black lines indicate extent of acoustic area as projected to lateral surface.

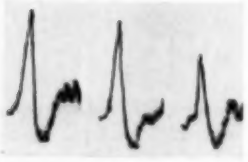

Fig. 2. Photographs showing typical cortical response to click stimulation.

presence or absence of response, since the variability in the response was unsystematic, even erratic.

The portion of the superior temporal gyrus of the monkey responsive to click stimulation was confined to the posterior half of the superior surface, adjacent to the insula. The area usually covers the medial half of the supe-

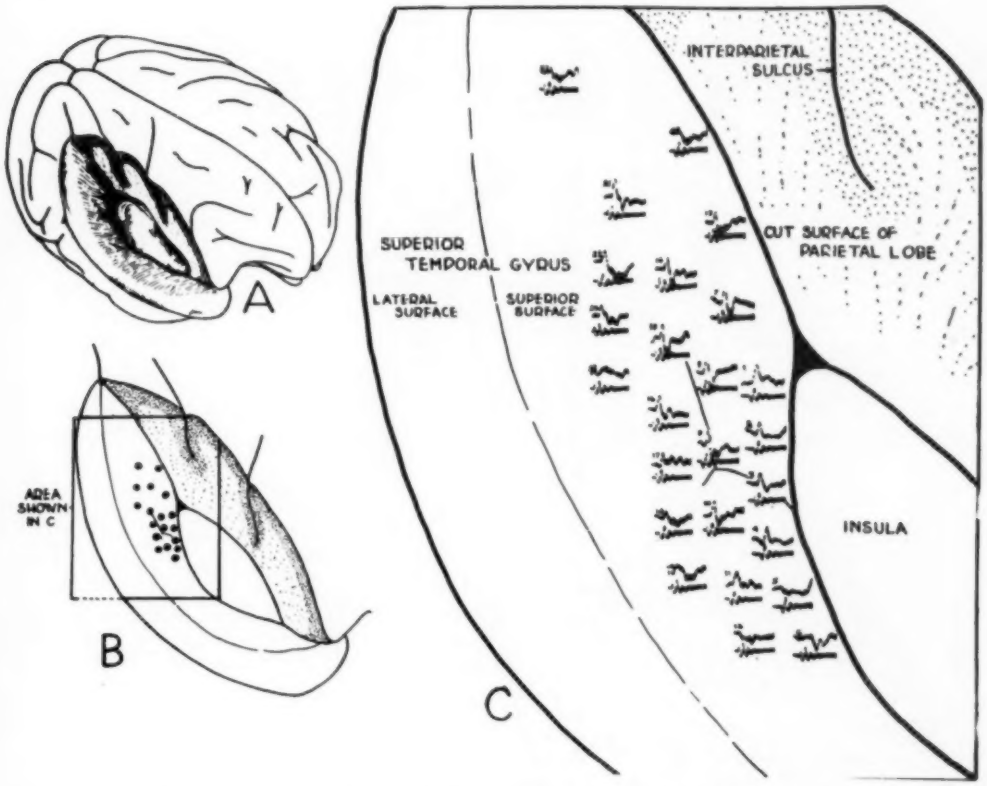

FIG. 3. Monkey No. 11, right side. A. Fronto-lateral view of brain, showing experimental exposure. B. Enlarged view of exposure; black dots indicate points from which responses were obtained. C. Enlarged view of area outlined in B, showing photographs of responses superimposed at point from which each was elicited. Lower trace in each case is the stimulus line.

rior surface, sometimes more, but never extends as far laterally as the exposed lateral surface of the gyrus.

Maximal responses were always from the angle formed by the posterior and medial margins of the superior surface, that is, from the medial end of the elevation referred to by Poliak, when the elevation is present. Responses diminish somewhat in magnitude as the electrode is moved farther from the angle, but the margin of the responsive area is marked by disappearance of response within a short distance. The gradient from center of responsive area to periphery is, therefore, not gradual, and from periphery to non-responsive cortex occurs an abrupt dropping-off of response. This is illus-

trated by Fig. 3 and 4, which show, on diagrams of the superior temporal gyrus of 2 monkeys, the responses at various points inside and outside of the area. In several instances it may be seen that adjacent points (approximately 2 mm. apart) give, at one point, marked response, and at the other, no response.

The area of responsive cortex is quite constant from one monkey to an-

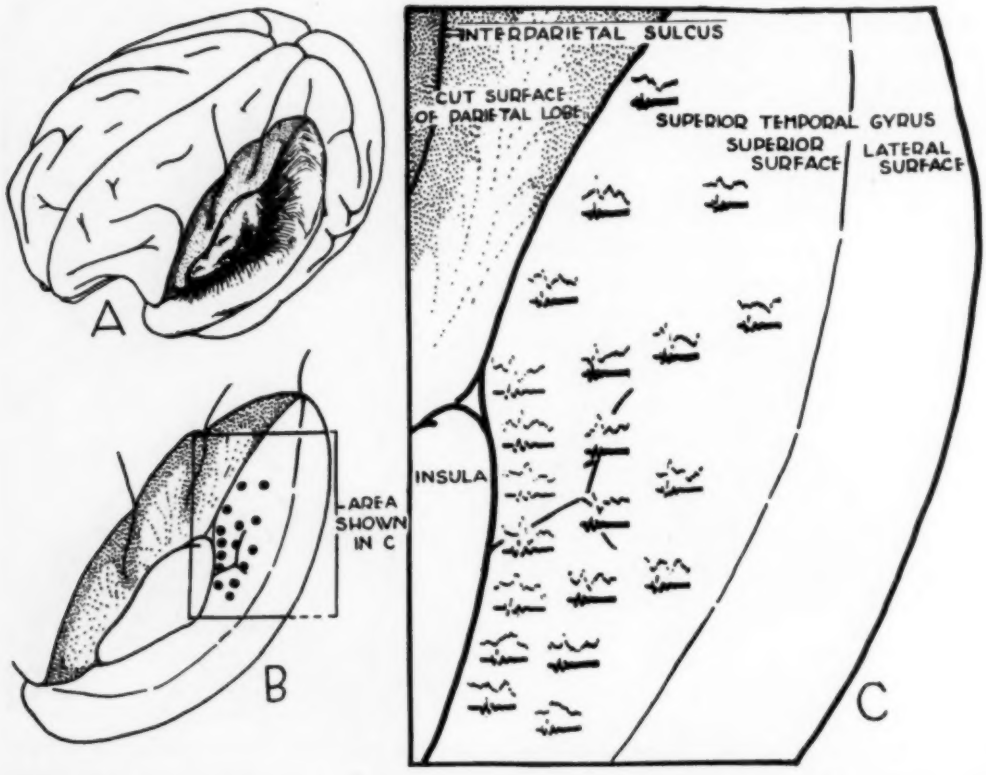

FIG. 4. Monkey No. 12, left side. A. Fronto-lateral view of brain, showing experimental exposure. B. Enlarged view of exposure; black dots indicate points from which responses were obtained. C. Enlarged view of area outlined in B, showing photographs of responses superimposed at point from which each was elicited. Lower trace in each case is the stimulus line.

other, as may be seen in Fig. 5. The angle of the medial and posterior margins, at the posterior extremity of the insula, which is the widest point on the superior surface, is always the approximate geographic center. The remainder of the area extends in either direction along the two margins for varying distances. It seems probable that if it were possible to place an electrode on the medial (vertical) surface of the superior temporal gyrus, one would also obtain responses there, since it is evident in most cases that the responses reach maximum at the medial border of the superior surface,

where the cortex turns to form the inferior vertical wall of the Sylvian fossa, opposite the inferior half of the insula.

No responses were elicited from the anterior half or the lateral-most strip of the superior surface of the superior temporal gyrus or from its lateral surface. The posterior extremity of the superior surface was also invariably

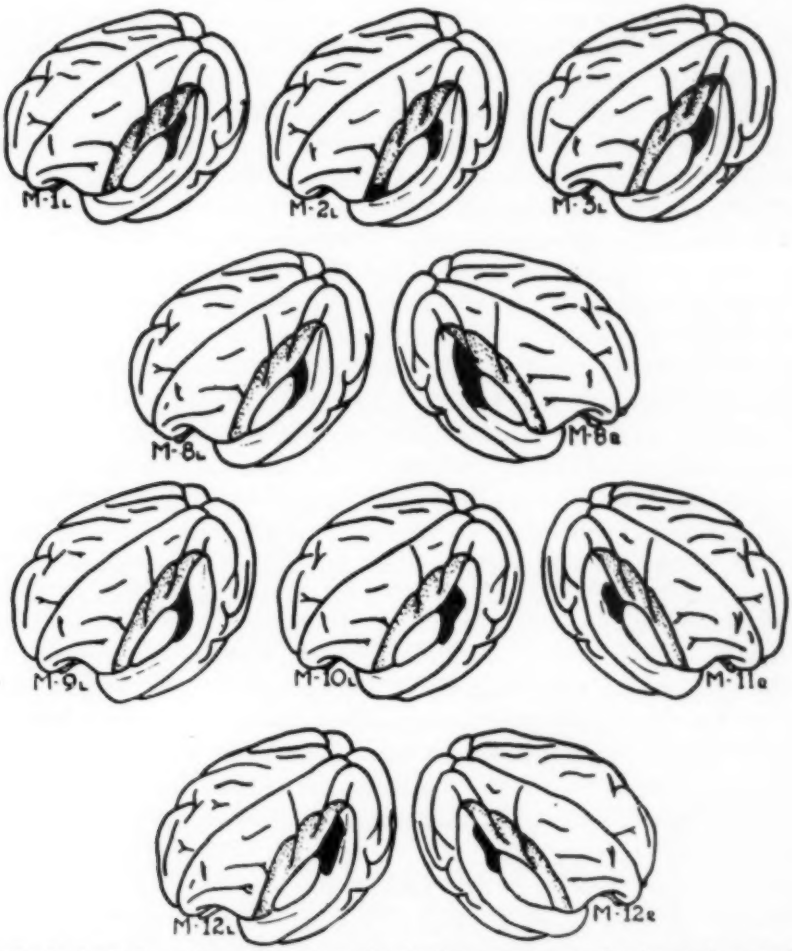

FIG. 5. Black-shaded portions indicate extent of responsive cortex in each case. Numbers indicate serial number of animal; small letters indicate right or left side.

silent to acoustic stimulation. This is apparently at variance with the anatomical findings of Poliak who described much more extensive endings of acoustic radiations, even to the lateral surface of the gyrus, and particularly to the posterior extremity. It is not easy to account for this apparent discrepancy. If it were possible to demonstrate a gradually diminishing magnitude of electrical response from a central maximum to a peripheral minimum, it would be easy to correlate magnitude of response with density

of innervation, since apparently Poliak's results indicate such a gradient of density of innervation. There is, to be sure, a border of less than maximally responding points around the periphery of the projection area, but the difference in magnitude of response between that border and the center of the area is not great, and two millimeters beyond the border the response drops out abruptly.

Walker states that the small temporal area, which he found to have the characteristics of koniocortex, ". . . is situated on a small elevation to which Poliak has previously called attention, and suggested that it might be a rudimentary transverse temporal gyrus." In the present study when the elevation is present, the medial half, which occupies the angle referred to above, is always responsive to click stimulation, whereas the lateral half is not. Furthermore, the responsive area nearly always overlaps the elevation both posteriorly and anteriorly. Thus, while part of the elevation is acoustic, part is not; on the other hand, not all of the acoustic responsive area is to be found on the elevation. These facts might indicate doubt that Poliak's elevation is truly a rudimentary transverse temporal gyrus. The question is of little importance, but it should be borne in mind that there is insufficient evidence to support the usual idea that the acoustic projection area is conterminous with Heschl's convolution. Similar experiments on the human brain might well show that there is a similar lack of absolute coincidence of transverse elevation and responsiveness to acoustic stimulation. There is no reason, therefore, to oppose Poliak's suggestion of homology between the transverse elevation of the monkey and the human transverse temporal gyrus.

Summary

By the method of recording cortical response to click stimulation, the acoustic cortex of the monkey has been mapped. The area responsive to clicks is the portion of the superior face of the superior temporal gyrus included in the angle between the posterior and medial borders of the gyrus. It varies in extent from 8 to 12 mm., and is consistent from one animal to another.

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THE BREAKDOWN OF ACCOMMODATION—NERVE AS MODEL SENSE-ORGAN

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IN EVERY highly developed sense-organ it is possible to distinguish a primary recipient mechanism, adjusted for maximal sensitivity to the adequate stimulus, and a secondary "generator" mechanism firing the nerve or perhaps ganglion cells directly. The very special problem as to how different forms of energy are translated into a physiological stimulus capable of exciting the generator mechanism will not be considered in this paper. We shall only be dealing with the nature of this secondary mechanism, a problem belonging to the general physiology of the special senses.

At present it is only possible to attack this general problem with the aid of hypotheses to be tested experimentally. The hypothesis to be chosen in the first instance is one which is suggested by the relatively extensive work on the retina. From this work it is known that the simpler the retina or the better the isolation of components of the response of complex retinae, the more definite the evidence for the conclusion that the generator mechanism is a slowly rising potential preceding excitation or inhibition, as the case may be (see Adrian and Matthews, 1928, Hartline and Graham, 1932, Hartline, 1938, Granit, 1933, 1938, Granit and Therman, 1935, Bernhard, 1941). There is enough evidence for the reasonableness of this general assumption to be found in the exciting properties of "local" potentials in nerve (Hodgkin, 1938), muscular end-plates (Göpfert and Schaefer, 1936), Eccles, Katz and Kuffler, 1941, Eccles and Kuffler, 1941), salivary glands (Langenskiöld, 1941), spinal neurons (Umrath, 1933, Barron and Matthews, 1938) to make the earlier results with the retina in no way exceptional. From the point of view of neurons and sense-organs, however, the main question is how repetitive firing is brought about by this potential difference. Thus "accommodation" enters the problem.

The work on accommodation shows that a non-accommodative nerve reacts to a rising current with a stream of impulses (Fessard, 1936, Erlanger and Blair, 1936, 1938) much as an adequately stimulated sense-organ would do, and that any nerve can be made to acquire such properties *e.g.* by suitable treatment with citrate or Ca-free Ringer (Solandt, 1935–36, Katz, 1936, Lehmann 1937, Schriever and Cebulla, 1938). It then tends to fire spontaneously. The same holds good for ganglions (Bronk, 1939) and sense-organs (Matthews, 1931 for muscle-spindle, Talaat, 1933 for sense-organs in the skin), many of which discharge spontaneously without having been subject to treatment of any kind. We have found (unpublished work) the retina also to increase its normal spontaneous activity after treatment with citrate-Ringer.

If sense-organs set up repetitive discharges as a consequence of "local"

potentials arising in them, then the question of *breakdown* of accommodation in nerve in response to slowly rising currents deserves a separate study. Beyond the general knowledge that a strong catelectrotonus causes a nerve to fire repetitively there is very little information concerning repetitive firing in normal vertebrate nerve. Such use of nerve as model sense-organ should show to what an extent imitation of the "generator" potential imitates some of the known properties of sensory discharges. Thus, for instance, the retina has a long latent period, 10–20 times any possible synaptic delay. It can react with excitation or inhibition, gives grouped or otherwise synchronized discharges, etc.

METHOD

For slowly rising currents of different time constants an apparatus built by our physicist, Mr. T. Helme, was available. The principle of this instrument is a release of an initially blocked anode current by charging the grid over condensers. Kahlson and v. Werz (1936) among others have utilized this principle before. An improvement in our apparatus consists in the use of a suitable resistance connected to the cathode-side of the H.T. circuit in order to eliminate deformation of the H.T. current rise owing to the characteristic of the valve. The form of the rise of the current in the stimulating anode circuit was determined oscillographically. In the diagrams plotted below, however, the actual rising times have not been used but a factor proportional to the $C \times R$ products of the condensers charging the grid. The reason for this was our original intention to calculate Hill's constant λ (Hill, 1936, and below). The stimulating currents remain at the level to which they have risen until broken off manually. A description of the technique together with observations on the breakdown of accommodation has been given in Swedish by Granit and Skoglund (1941).

Silver-silver chloride electrodes placed in the anode circuit were held to be satisfactory on account of the high internal resistance of the H.T. circuit relative to that of the tissue. The nerves were stimulated monopolarly through these electrodes. A Lapicque-circuit similar to the one used by Solandt (1935–36) for slowly rising stimuli was also available.

Decerebrate cats, sometimes frogs, were used for work on peripheral nerve. In the former case the animals were kept in a heated and shielded box with a cistern of boiling water supplying the moist atmosphere needed. A number of experiments were also carried out with the retina and optic ganglion of *Dytiscus*.

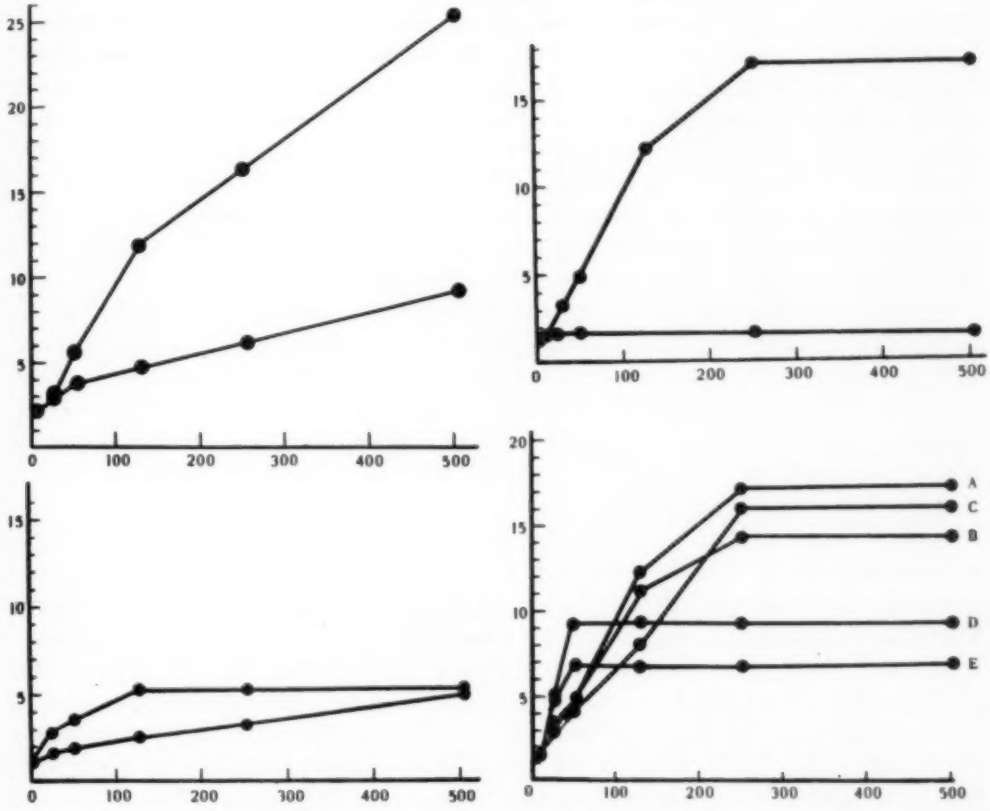
Cathode ray oscillograph and condenser coupled amplifier were used for recording from nerve or muscle.

RESULTS

1. *The index for accommodation measurements*

In 1884 it was shown by von Kries that, as the rate of rise of the stimulus decreased, the currents had to be made stronger in order to excite. He also plotted curves showing current strength as ordinates against rising time as abscissae. Following Hill's (1936) theory Solandt (1935–36) and Katz (1936) plot their results in the same manner but using multiples of rheobasic strength as ordinates and a factor proportional to rising times as abscissae. As a consequence Hill's accommodation constant λ appears as the inverse value of the slope of these curves which for the short rising times in which they were interested were rectilinear. Thus, with little accommodation, λ is great, the curves approach horizontality, and the nerves even tend to fire repetitively (Katz, 1936). Index in these measurements was a threshold muscle contraction.

In actual practice these measurements may be made in several different ways and we also began by using a threshold muscle contraction as index and determined the current strength necessary for a given rate of rise. Such experiments showed that what we have called "breakdown" of accommodation can be demonstrated already by observing the curves obtained in this



FIGS. 1–4. "Accommodation curves" for mammalian nerves with threshold muscle contraction as index. Abscissae: Rising time of stimulus in msec. (see text). Ordinates: Multiples of rheobase. Rheobase unit = 1 in all curves, but curves not always continued to this unit. *Fig. 1:* upper curve transected sciatic, lower curve transected peroneal nerve. *Fig. 2:* upper curve, unsevered peroneal nerve, lower curve, *n. aurient. magn. Fig. 3:* A–C: unsevered peroneal nerve, A immediately, B after 4 min., C after 25 min. D–E: same nerve severed and electrodes near cut end. *Fig. 4:* severed sciatic: upper curve electrode about 4–5 cm. from cut end, lower curve at cut end.

manner. Some curves selected from a large number of experiments are given below.

Figure 1 shows two curves for the sciatic and the peroneal nerve, both severed, Fig. 2, two intact nerves, *n. peroneus* and *n. auricularis magnus*, in the latter case with a reflex muscle contraction (pinna reflex) as index. The auricular nerve generally gave curves of this type. In Fig. 3 the three upper curves (A, B, C) were taken in this order during half an hour with the elec-

trode on an intact peroneal nerve. Then the nerve was severed and the electrodes placed near the cut surface. The curves D and E were obtained. The results are typical. Finally, in Fig. 4, a sciatic nerve, sectioned from the beginning, was used, but at a relatively late stage, the lower curve showing the result of putting the stimulating electrode near the cut end of the nerve.

According to Hill (1936) and his collaborators, whose interest was restricted to the early part of these curves, the inverse value of the slope is a measure of accommodation. Thus, the more the curves approach horizontality, the less the capacity of the nerve to accommodate. At the outset we shall define complete breakdown of accommodation by taking from the diagrams the strength of current at which the curves turn round to become horizontal. Beyond this point the nerve responds to any current above the strength of this ordinate independently of its rate of rise. In the sample curves of Figs. 1–4 breakdown occurs with different degrees of completeness and at different strengths in terms of multiples of rheobase.

A glance at these curves shows that accommodation in mammalian nerves is extremely sensitive to interference with the tissue (cf. also Schriever 1932, Liesse, 1938, a, b for blood supply etc. and frog nerve.) But there must also be unknown physiological factors to account for variations which certainly are not caused by maltreatment of the nerves. It seemed worth while investigating whether such variations had something to do with the observation that the muscle contraction was an unsatisfactory index. For rapidly rising currents the threshold contraction was brief and precise, but with slowly rising stimuli it also became slow, looking then more like a contracture. Hoffmann in 1910 had already found that the action currents then indicated repetitive firing. Schriever and Cebulla (1938) have repeated and confirmed these observations using frog's nerve which apparently in the normal state accommodates much better than mammalian nerves.

In repeating this work with leads to the amplifier from the stimulated nerve we found that the index for accommodation was equally uncertain in this case. There is no doubt repetitive firing from the nerve (cf. also Rosenblueth, 1941), developed more with slowly rising stimuli, but the question as to when and how the breakdown of accommodation takes place, is still unsolved, except that it is clear that, as predicted by Hill's theory (1936), in a general manner there is less accommodation when the slope is smaller. But it is obvious that the difficulty of deciding whether a brief or a protracted muscular contraction should be used as the constant index, necessary for obtaining the accommodation curves, is by no means solved by exchanging it for the difficulty of deciding what kind of nervous discharge to use as index, since the latter also is far from being constant but varies with respect to duration, number of spikes and amount of potential. For whole nerve such records have been published by Schriever and Cebulla (1938) who also found in frog's nerve the bend of the curve noted by us, although it was not so marked.

2. *Accommodation in motor units*

The next step in the work clearly required some kind of restriction of the activity to smaller populations and the simplest method (Skoglund, 1942) seemed to be to insert fine electrodes in the muscle. Silver pins in a glass tube, drawn out in a flame with the glass to a thin point, were used as different electrodes (*musc. tib. ant.*, cat) the indifferent electrode being on the bone clamped to the myograph drill. The stimulating electrodes were on the peripheral stump of the severed sciatic.

To judge from the literature on "muscle spikes" many workers are under the impression that small electrodes restrict the discharge to single motor units. But it can easily be shown, if a motor nerve be stimulated with a neon-stimulator at different strengths, that the seemingly isolated spikes of activity of constant size increase in size within a range of

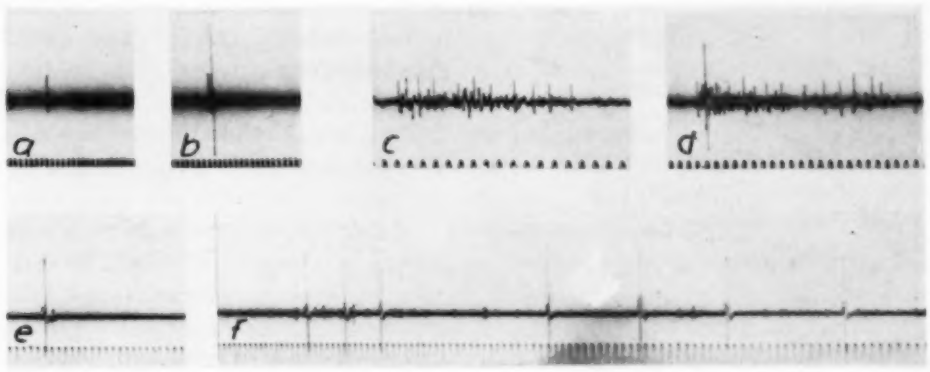


FIG. 5. Spikes recorded with microelectrode in cat's *tib. ant.* and stimulating electrodes on severed sciatic nerve. Time in 1/50 sec. Full description in text. (We regret that good films have not been obtainable.)

10 times or more when the stimuli are strengthened. Obviously therefore synchronized activity can throw into action a greater or smaller number of muscle fibres and we have no means of deciding by merely relying upon the electrode whether these fibres belong to the same motor unit or not. The all-or-none law is no reliable criterion since well synchronized spikes keep constant for a given current strength. The same holds good for recording with concentric needle electrodes (cf. Blake, Pritchard, 1930). Despite this microelectrodes are a definite improvement and some restriction of activity is obtained with them.

With this method one of us (C. R. S.) found that the motor nerve typically activates small or large spikes in the muscle (see Fig. 5) and that these have different properties with regard to accommodation. His analysis of the properties of the "spike patterns" will be published separately (Skoglund, 1942), and we shall here merely discuss *breakdown* of accommodation in relation to this new index of activity.

Figure 5a shows a single small spike at relative threshold-strength 8 and time 10, in fact the first point plotted on the lower curve of Fig. 6. Keeping the same spike as constant index this lower curve was traced in the usual manner. If at 10 msec. the strength of current was increased, the response b of Fig. 5 was obtained. This shows a large spike. The small spike now

reacts repetitively. But it is of course also possible to trace an accommodation curve with the single large spike as index. This is the upper curve of Fig. 6. The kind of response obtained for 20 msec. with the large spike at the threshold is shown in Fig. 5d. Somewhat below the threshold for the large spike, that is at strength 9.5 for 20 msec., only small spikes are seen, and there is definite repetitive firing (5c).

It would be a mistake to believe that only the small spikes are repeated. The lower curve of Fig. 5 is from another experiment, in which for 200 msec. a large spike appears at the threshold (e). The small spikes are here very small. Record f shows a small increase of current strength, from 35 in record e to 40 in f. The large spike now has become repetitive. Thus, it is only necessary to increase current strength for a given rate of rise a little above the value given by the ordinate on the accommondation curve to find a repetitive discharge in the nerve.

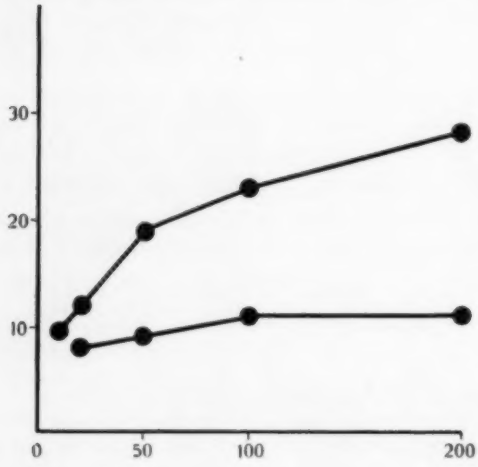


FIG. 6. "Accommodation curves" with (lower curve) small spike (a in Fig. 5) and (upper curve) large spike (b in Fig. 5) as index. Abscissae as in Fig. 1–4. Ordinates: relative current strength (*not* multiples of rheobase) in order to show relative threshold.

Accepting the result of Skoglund's (1942) analysis, *viz.* that the difference between large and small spikes depends upon the degree of "grouped action" of the stimulated fibres, we have now to reconsider repetitive firing and the breakdown of accommodation from this point of view. It is clear that *in general* repetitive firing takes place in the region above the accommodation curve, provided that relatively slowly rising stimuli be used. This proviso is necessary because with strong and rapidly rising stimuli there is an *alternative* to repetitive firing in the possibility of grouped action, or, rather, increased degree of grouped action, the small spikes probably also being due to smaller groups. The consequence of this alternative is that it is possible to plot a new and steeper accommodation curve for the grouped fibres with consequent smaller value for λ. Breakdown of accommodation as well as accommodation itself is therefore influenced by the manner in which the fibres co-operate.

The new "constant" λ which, as we now may suggest, is constant only for relatively brief rising times means that the grouped fibres resist breakdown better than relatively isolated elements,—a conclusion with many significant consequences, among them that the theoretically correct value for λ with mammalian nerves can be obtained only with isolated fibres under the electrodes.—From the point of view of sense-organs we must conclude

that *an end-organ, developing generator potential, has a much better chance of causing breakdown than any electrical stimulus over a group of elements. It has a chance of exciting a single axon in a highly adequate manner by electrotonic spread designed to minimize accommodative resistance.*

Returning now to the curves of Fig. 1–4, obtained in the usual manner with a threshold muscle contraction as index, it is clear that the variability which is so obvious a feature of such measurements to a large extent must be due to the uncertainty of the index which in turn also depends upon the degree of "grouped action," a factor so far definable only with respect to the strength of the stimulus but probably influenced by a number of other variables, among them temperature, maltreatment of the nerve etc. Thus, it is reasonable to suggest that, when in Fig. 3 a shift of the stimulating electrodes to the cut end of the nerve leads to steeper initial rise of the curves followed by sudden breakdown of accommodation, the cause behind this change is, that grouped action with consequent steeper rise is favoured by the injury potential but that at the same time the strength of catelectrotonus necessary for complete breakdown has decreased.

This raises the question as to what extent the breakdown obtained with mammalian nerves is a normal phenomenon. The small and large spikes, forming a whole "spike spectrum" and the main phenomena are certainly obtained also with unsevered nerve, just isolated and put on the electrodes. But there is no doubt but that breakdown of accommodation and small slopes of the curves are favoured by a departure of the nerve from "normality."

3. *Definition of breakdown of accommodation*

In the discussion following upon the publication of Hill's theory (1936) it has been emphasized by M. and L. Lapicque (1937, a, b, 1938) that the autorhythmic activity of nerve may have complicated measurements of accommodation, particularly in citrated-nerve, and that stimuli of long duration alter the state of the tissue. The latter objection need not be true. If care be taken to preserve an accurate index of accommodation the curves obtained with mammalian nerves are constant for hours.

But the rhythmic activity does introduce complications (cf. v. Kries, 1884, Hoffmann, 1910, Schriever and Cebulla, 1938) inasmuch as it complicates evaluation of the index, and probably, as held by Fabre (1931, 1936), represents a physicochemical system with properties very different from those tested by the usual shock technique. It is no exaggeration to state that this latter technique, as applied to whole nerve and muscle, has served to keep the facts connected with repetitive firing out of focus.

From the point of view of the problem "generator potential-repetitively firing axon," so clearly raised by all the work on the retina (cf. particularly Bernhard, 1941), the breakdown of accommodation in nerve is of interest as a model. Its definition by the aid of our results is based on the change of slope of a curve which *as a whole* serves to characterize these properties of the excitable tissue. The inverse value of the initial part, Hill's constant λ,

may still serve as a useful approach to many problems as it has done to our own work. Looking very generally upon accommodation as a process tending to counteract the effect of a maintained stimulus, our curves mean that this process, so to speak, breaks down during the time the stimulus is applied, provided that it has reached a certain level of strength, and that finally there is so little accommodation left that the stimulus always excites, no matter how slowly it reaches this level. The slope of the curve then becomes horizontal. By following our curves far enough we reach the point when catelectrotonus excites independently of and not counteracted by accommodation. Above our curves lies the region of repetitive firing of the particular single unit or grouped unit concerned. We do not believe ourselves that spikes of the small type represent single fibres.

4. *Inhibition*

In looking for a model reproducing retinal inhibition it has been necessary to discard the idea that it could be explained as a subnormal phase according to Gasser (in Erlanger and Gasser, 1937). In 1935 Granit and Therman showed that inhibition of the discharge in the optic nerve is preceded by a slow potential belonging to the component PIII of the retinal response. This result was subsequently confirmed by Hartline (1938). A full discussion of retinal inhibition is found in a summary by Granit (1938). Since then Therman (1938) has shown that the retinal component does not agree with subnormality by any of the chemical tests selectively influencing the positive after-potential. Bernhard and Skoglund (1941) have found that alcohol selectively diminishes the negative component PIII and that at the same time inhibition also diminishes. The connexion between PIII and inhibition has thus been confirmed. This does not necessarily mean that PIII could be excluded as factor causing excitation. This potential precedes PII at both "on" and "off" as we have now definitely proved (Bernhard, unpublished work).

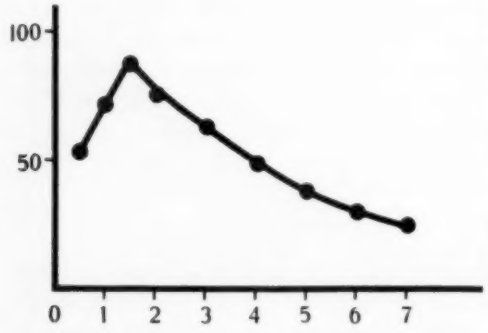


FIG. 7. Frequency of discharge in frog's nerve following removal of anelectrotonic block. Abscissae: time in sec. Ordinates: frequency per sec.

If PIII were an anelectrotonic state developing during illumination, then the off-effect could be regarded as the consequence of the release of anelectrotonus which during illumination had piled up inhibition influencing certain retinal neurons. Our model would then be an anelectrotonic block. Actually, after an anelectrotonic block across a frog's nerve, the impulse frequency of the ensuing discharge often follows a curve of the type given by the retinal off-effect. This is shown in the example of Fig. 7.

On the other hand, it is known that a sufficiently strong catelectrotonus also may block nerve fibres (see *e.g.* Bugnard and Hill, 1935). In our experiments catelectrotonic inhibition has often been seen when for some reason or other the nerve fires spontaneously as in the record of Fig. 8. Here the discharge is inhibited by a catelectrotonus. The component PIII could also just as well be imitated by this model. It is known that the retina is oppositely influenced by opposite polarizing potentials across it (Granit and Helme, 1939). At the moment it is hardly necessary to go beyond the general hypothesis that a generator potential, capable of causing excitation, may also be capable of causing inhibition. Below we shall show that the same polarizing current gives excitation *or* inhibition in the optic ganglion of *Dytiscus* depending upon whether it is silent or discharges spontaneously at the time of applying the current.

5. *Latent period and adaptation*

Both phenomena are reproduced by the model. The slower the rise of the current the later the initiation of the iterative discharge. This follows directly

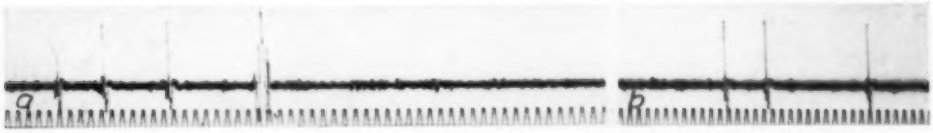


FIG. 8. Spontaneous discharge (a) in cat's *tib. ant.* muscle. Catelectrotonus on sciatic nerve leading to an outburst of muscle spikes followed by inhibition for the time the stimulus remains on. Afterwards (b) renewal of spontaneous discharge.

from the fact that a certain minimal strength of current is necessary for it, and that it is possible, by delaying the rate of rise of the current, to postpone the moment at which this level of excitation is reached. When passing beyond the strength of current necessary for iterative firing anywhere above the accommodation curve, it is seen that iterative firing does not continue indefinitely but stops after some time (Skoglund, 1942). There is thus a parallel to adaptation, which, of course, in addition may be determined by the properties of the primary mechanism which precedes the generator potential of the end-organ.

6. *Application of model to eye of Dytiscus*

The primary visual cells of both vertebrate and invertebrate eyes are homologous and have been carried through the whole progress of evolution (Kappers, Huber, and Crosby, 1936). In the water-beetle Bernhard's recent work (1941) has shown that the visual cells easily can be separated from the optic ganglion lying behind them and that the isolated retina gives a large smooth action potential reminiscent of the simple response of *Limulus* (Hartline, 1928, Hartline and Graham, 1932), and preceding the discharge in the nerve. If the ganglion is included spikes or synchronized waves appear on the response (cf. Adrian, 1932, 1937).

Where in this sense-organ are impulses generated? In order to answer this question we attempted to record from various parts of the retina by means of microelectrodes, *e.g.* through openings in the chitinous cover of the lenses and from behind. But from nowhere in the retina can any trace of impulses be obtained, not even if the microelectrode is forced in between optic ganglion and retina with tip towards the latter. In contradistinction to this stands the fact that impulses are obtained practically everywhere from the ganglion or on the optic nerve emanating from it.

From the work of Granit and Therman (1938) and that of Bernhard (1940, 1941) we know that the large potential difference developing across

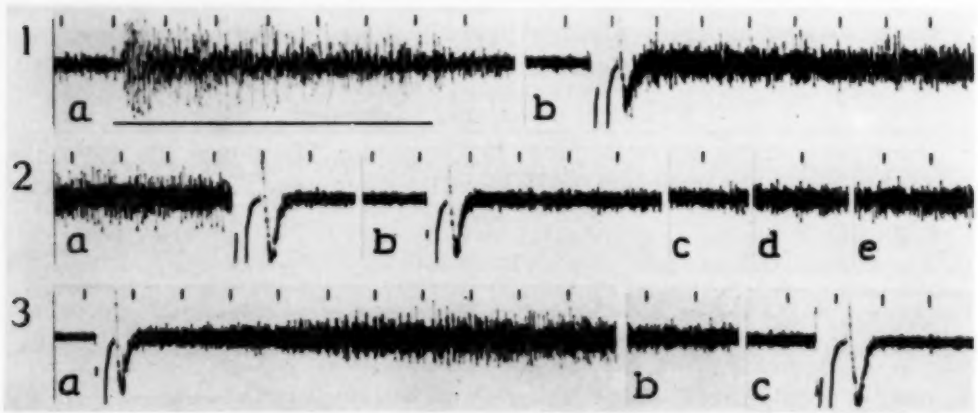


FIG. 9. Eye of *Dytiscus*. 1a, whole eye illuminated, optic nerve. 1b, isolated silent ganglion stimulated cathodally (at artefact). 2a, activity in isolated spontaneously active optic ganglion inhibited by cathodal stimulation, 2b, removal of catelectrotonus, 2c, d, e, f, gradually recovering spontaneous discharge. 3a, silent isolated optic ganglion stimulated anodally, 3b, gradual diminution of frequency, 3c, removal of anelectronus. All records taken with small metal electrodes. Time in $\frac{1}{4}$ sec.

the retina upon illumination is carried down electrotonically to and over the ganglion. On our hypothesis this would serve as generator mechanism for impulses, provided that the threshold for breakdown of accommodation were low. That this must be the case is shown by the tendency of the eye to discharge spontaneously. Fig. 9 shows an experiment with a cathode or anode on the ganglion isolated in air and the other electrode on the supraoesophageal ganglion. Microelectrodes are used for picking up the impulses from the ganglion.

First follows a control with illumination (1a) showing that the retina was alive before isolated from its ganglion. There is a small spontaneous discharge before illumination sets in. After separation from the retina the optic ganglion is stimulated cathodally with anode on the supraoesophageal ganglion. This leads to a discharge (1b). Record 2a shows another spontaneously active ganglion. Cathodal stimulation in this case immediately blocks the discharge which slowly reappears when the current is cut off (2b, c, d, e). Finally anodal stimulation (3a) is applied onto another isolated optic gan-

glion which was silent from the start but began to discharge upon stimulation. This discharge gradually diminished and did not reappear when the stimulus was removed (3c).

Now a preparation of this type consisting of ganglion cells surrounding a bundle of nerves emanating at one end as an optic nerve cannot be precisely stimulated anodally or cathodally. But the experiments nevertheless show that in both cases both inhibitory and excitatory effects were obtained. The only rule observed was the one illustrated, *viz.* that silent ganglions began to discharge and active ones were inhibited by the polarizing current.

Actually in this eye both effects are also observed by stimulation with light. When the "generator" potential develops across the visual cells upon illumination, there follows a heavy outburst of impulses which instantaneously stops at "off." But if the preparation is discharging spontaneously it can be seen that the drop of potential at "off" leads to an additional slow potential from the ganglion accompanied by a temporary inhibition of the spontaneous discharge (Bernhard, 1941). It is therefore possible that the abrupt stop of the normal discharge following cessation of illumination also is brought about by active inhibition.

These experiments together with those of Bernhard (1941b) show: (i) the sensory cells themselves develop only generator potential but no impulses, (ii) the generator potential is carried down electrotonically to the optic ganglion, where both a slow stationary potential difference as well as an impulse discharge is initiated, (iii) in some cases inhibition turns up instead of excitation, and (iv) these phenomena all can be imitated by polarizing currents (cf. also Granit and Helme, 1939). Whether the large potential difference across the sensory cells initiates impulses directly or *via* the slow potential in the ganglion cells (Bernhard, 1941), cannot be discussed without further experimentation.

Other sense-organs may be working on the same principles, unless so primitive that breakdown of accommodation takes place directly in free thin nerve-endings influenced by changes in ion balance or the concentration of surface-active substances released around them. (*e.g.* pain).

Summary

The work described serves the twofold aim of clarifying some elementary questions regarding accommodation in nerve relative to repetitive firing and of finding out to what extent a nerve discharging repetitively in response to slowly rising electrical stimuli can serve as model sense-organ.

"Accommodation curves" obtained by plotting rising time of the stimulus (to a motor nerve) as abscissae against multiples of rheobase as ordinates for a constant effect show that a muscle contraction or a discharge from whole nerve are unsuitable as indicators for the constant effect.

Nevertheless, also with this effect as index, it is clear that for slowly rising stimuli the nerves may cease to accommodate, that is, that breakdown of accommodation takes place.

In order to obtain a better defined index, microelectrodes were inserted in the muscle and isolated spikes, elicited by stimulation of the motor nerve with slowly rising currents, are used as the constant index necessary for measuring accommodation correctly.

Breakdown of accommodation is shown to take place also with this index and is redefined in terms of the properties of single spikes. It is shown that "grouped activity" in which several fibres fire synchronously is an alternative to breakdown or accommodation and that the accommodation curves are determined by the degree of interaction of the stimulated fibres.

In the region above the accommodation curves the nerves fire repetitively.

Not only anodal but also cathodal polarization caused by the slowly rising stimuli is capable of inhibiting a spontaneous discharge in the nerve.

The significance of these results is discussed from the point of view of nerve as model sense-organ on the assumption that a slow "generator potential" is the mechanism which in sensory end-organs fires the axon repetitively.

Application of the model to the retina and optic ganglion of *Dytiscus* shows that both excitation and inhibition may be obtained by anodal and cathodal polarization of the ganglion and that no impulses but only a slow potential is generated within the isolated retina of this animal. A silent isolated optic ganglion is excited, and a spontaneously firing one, inhibited by the polarizing current.

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THE EFFECT OF SECTION OF THE MEDIAL LEMNISCUS ON PROPRIOCEPTIVE FUNCTIONS IN CHIMPANZEES AND MONKEYS

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INTRODUCTION

THE ANATOMICAL observations of Le Gros Clark (1, 2) and Walker (8) have demonstrated the course and termination in the primate thalamus of the fibers of the medial lemniscus and dentato-rubro-thalamic tract. These tracts constitute separate afferent pathways which end discretely in the latero-ventral nucleus of the thalamus whence they are relayed to the cortical post and pre-central areas respectively. While both systems are known to carry proprioceptive impulses, the functional relationship of the fillet and the cerebellar projection to the thalamus has not been established. In the present paper an attempt was made to study the alterations in the proprioceptive skill and weight discriminatory ability of chimpanzees and monkeys following interruption of these tracts and to compare the resulting deficit with that observed after lesions at other sensory levels of the central nervous system.

METHOD

In two chimpanzees and eight *Macaca mulatta* the left medial lemniscus was sectioned at the level of the inferior colliculus, just rostral to the decussation of the brachium conjunctivum. In two mangabeys, *Cercocebus torquatus atys*, the superior cerebellar peduncle bearing the dentato-thalamic fibers was severed. In one chimpanzee and several of the macaques with interruption of the mesial fillet, the ascending dentato-rubrothalmic tract was also involved. All operations were carried out under sodium amytal anaesthesia with sterile technique and the animals were observed for periods ranging from three weeks to eighteen months.

The chimpanzees, mangabeys, and one macaque, "Dynamite," were trained to discriminate weights according to the technique described by Ruch (6, 7). Pre- and postoperative limens and comparison of the normal and affected limbs after operation, afforded a quantitative index of this proprioceptive function. Clinical observations of running, climbing and cage activities as feeding and grooming, furnished valuable indications of the measure of proprioceptive skill. Placing and hopping reactions were studied in all of the monkeys, as was the "voluntary" grasp response to the placing of the examiner's finger in the animal's hand or foot. Observations were also made of changes in motor power, resistance to passive motion, reactions to thermal and painful stimuli, pupillary changes and disturbance of piloerection.

All operative lesions were verified by histological examination. The Weil and Nissl methods were employed in most cases. Four monkeys were sacrificed at the end of 21 days for study of Marchi degeneration.

OBSERVATIONS

The principal observations are covered in the following protocols. *Experiment 14. Section of left medial lemniscus and lateral spinothalamic tracts. Sparing of dentato-thalamic fibers.*

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Persistent hemianalgesia. Marked initial defect in proprioceptive function which rapidly improved. Ability to discriminate weights normal two months after operation (Alice).

The subject of this experiment was a healthy, docile young female chimpanzee.

First operation: On August 3, 1939, under sodium amytal anaesthesia, the left mesial lemniscus was severed at the level of the inferior colliculus. The temporal lobe was elevated, the cisterna ambiens opened, and a stab made just dorsal to the groove separating the cerebral peduncle from the tectum mesencephali.

Postoperative notes: On the first postoperative day the chimpanzee was able to move its right limbs slightly, but could not grasp. The right extremities could be placed by the examiner in any awkward position, without the animal correcting the abnormal posture. The deep reflexes were not increased and there was no Babinski. The animal did not respond to pinprick over the entire right side of the body and face, while a much more gentle stimulation on the left caused vocalization and prompt withdrawal. Examination of the cranial nerves showed the corneal reflexes to be present bilaterally, but somewhat diminished on the right. The left pupil was larger than the right and there was an apparent right sided hemianopia. There was a horizontal nystagmus with the quick phase to the left. A slight supranuclear facial weakness was seen. In the next few days the hemianopia, nystagmus and facial weakness disappeared. The sensory deficit persisted, while there was a rapid return of motor power. The right limbs were moved well, but were of little use in feeding and climbing, apparently due to a loss of touch and position sense. The chimpanzee was able to walk but did so with a characteristic high stepping of the affected extremities. There was still no response to pinprick and pinching of the right side. No change in resistance to passive motion of the limbs was noted.

The subsequent three weeks saw a progressive return of proprioceptive function. The animal grasped with either hand. It could, one month postoperatively, manipulate even a small bit of peanut in acceptable fashion. Gait still showed a slightly higher stepping with the right leg. The animal was fond of trying to slip a key into a lock and regained its skill at this. Six weeks after operation, training in weight discrimination was resumed and the animal soon performed at the preoperative level.

The animal died on January 11, 1940 after an attempt to add to the proprioceptive deficit by sectioning the right superior cerebellar peduncle. The brain stem was sectioned serially and studied by the Weigert and Nissl methods. At the level of the inferior colliculus, the left mesial fillet was sectioned except for the narrow mesial tip; the left lateral spinothalamic tract was completely interrupted. There was a slight amount of damage to the brachium conjunctivum at the rostral part of the decussation. The pyramids were spared. There was also injury to a few of the fibers of the left third nerve. In sections up through the level of the red nucleus, the left medial meniscus was seen to be completely demyelinated.

Experiment 15. Section of left medial meniscus and ascending dentato-rubro-thalamic fibers. Intention tremor of left arm. Permanent deficiency in proprioceptive skill and ability to discriminate weights. Slight right hemihypalgesia. (Johnnie.)

The subject of this experiment was a playful young male chimpanzee.

First operation: On August 7, 1939, a left-sided, mid-brain tractotomy was attempted. The following day, it was apparent that the ascending sensory tracts had not been interrupted as the animal used both hands well and responded promptly to pinprick stimulation. Accordingly, the chimpanzee was reoperated.

Second operation. On August 11, 1939, under sodium amytal anaesthesia, the flap was reopened and the stab in the midbrain exposed and enlarged to a depth of 10–11 mm. The animal withstood this second procedure excellently.

Postoperative notes. On the first postoperative day, the right limbs hung limply, with diminished resistance to passive movement, though the animal was able to use them to some extent as a support. In attempting to walk, it tended to drag the affected extremities along after it. Voluntary grasp was absent in the right hand and abnormal postures were not corrected. The rest of the sensory status was difficult to evaluate. The chimpanzee was frequently seen to scratch the right side of its body as if there were some paresthesia. Pricking the right limbs with a pin resulted in a delayed response, while several seconds after the application of the stimulus the animal would rub the affected spot. On the left side there was prompt withdrawal to any noxious stimulation.

The disability of the right limbs persisted, though it was evident that this impairment was not due to motor weakness as the animal moved all four limbs well. In resisting dis-

agreeable procedures, as a scrubbing for a skin infection, it struggled powerfully. On September 13, 1939, one month after the second operation, the following note was made: "There is marked disability of the right limbs. The animal is able walk and climb about the cage but the right limbs are of little assistance. In walking, the right upper extremity is carried in flexion at the elbow, the hand swings flail-like at the wrist, while the right lower limb is raised high in an exaggerated stepping. In climbing, the subject repeatedly misses its footing with the affected hand and foot. It gets into awkward positions with the right leg bent back behind it. It does not take food with the right hand or grip the examiner's fingers. In attempting these acts, an intention tremor of large amplitude is present. There appears to be diminished resistance to passive motion in the right limbs. The animal apparently perceives thermal and painful stimuli over the right side of the body, though the responses are diminished compared to the left. The spinothalamic sensory deficit is not as severe as in chimpanzee Alice. The withdrawal movements illustrate the good motor power of the right limbs. The knee jerks are lively and active. The left pupil is larger than the right."

The animal was disinclined to use the right limbs but when forced to do so began to show a slight improvement. It became able to grasp and could clumsily convey food to its mouth, but could not manipulate small objects as a peanut kernel, with which it would fumble. The intention tremor persisted.

Preoperative training had resulted in the chimpanzee discriminating a 40 per cent weight difference 98 per cent correctly, and a 20 per cent weight difference with a score of 92 per cent. One month after the operative procedure, Johnnie was only 60 per cent correct at a 40 per cent weight difference, and at a 30 per cent difference gave a 50 per cent score. Despite the intention tremor and the clumsiness, it was able to effectively grasp the cannisters containing the weights, so that the motor disability was not responsible for the defect.

Experiment 21. Section of left superior cerebellar peduncle. Marked intention tremor and ataxia of left hand. No loss of manipulative skill and ability to discriminate weights. Placing and hopping reactions retained.

The subject of this experiment was a male sooty mangabey (*Cercocebus torquatus atys*) weighing 3400 grams.

First operation. On October 31, 1939, under sodium amytal anaesthesia, the left superior cerebellar peduncle was severed. The cisterna ambiens was opened and the peduncle cut as it entered the brain stem.

On the first postoperative day, the animal did not use the contralateral (right extremities) which were dragged about the cage. There was a severe intention tremor and ataxia of the homolateral left upper limb. When the animal attempted to convey food to its mouth with the left hand, it would often hit itself in the right eye. When the left arm was supported, however, the monkey was able to pick up small objects and manipulate them quite well.

A right-sided visual field defect was present. This cleared up along with the right hemiparesis after two or three days. A progress note of November 7th read "The severe left-sided ataxia, dysmetria and intention tremor persist. In running, the left limbs swing wildly. Placing and hopping reactions are present bilaterally. The animal uses the right limbs to hold the left hand and control the tremor. When this is done it is seen that the monkey is able to manipulate bits of food in acceptable fashion. Training in weight discrimination was resumed one month after operation. Despite the ataxia and intention tremor, there was no change from the preoperative level."

Section of Medial Lemniscus in Monkeys

In the macaques, the following observations were made after section of the left medial lemniscus at the midbrain level.

On the day after operation, the monkey sat in its cage with its head inclined to the right, the chin slightly rotated to the left. There was a transitory rotary nystagmus, which with the abnormal head posture cleared up in two or three days. The limbs contralateral to the lesion hung limply with obviously complete loss of propioceptive function. The affected arm and

leg fell into awkward postures or became entangled in the wire mesh of the cage without any attempt at correction.

On the fifth postoperative day, the animal was released from the cage and allowed to run down a long corridor. Here a right sided visual field defect was apparent as the monkey repeatedly collided with the right wall. There was a characteristic, high stepping, galloping gait in which the right limbs were flung in a high arc. Climbing was performed poorly, the animal missing its perch with the right limbs. This clumsiness was best observed when the left normal limbs were restrained and the animal forced to feed itself with the right hand. The monkey would have great difficulty in grasping even a large morsel, fumbling, and being quite unable to manipulate it. This disability could not be attributed to weakness, as there was good power in the affected limbs as observed when the animal struggled to free itself from restraint.

The degree of recovery in the affected limbs after section of the mesial fillet appeared to depend, as in the chimpanzees, on the extent of the additional involvement of ascending dentato-thalamic fibers. In the macaques in whom there had been no damage or only slight implication of the brachium conjunctivum, there was a rapid return of function, so that three weeks after operation, only a slight proprioceptive defect remained. There was some disinclination to use the affected extremities with a tendency to overstepping still noticeable in the gait. The animals climbed well, though the surefooted scampering and abandon of the normal macaque had given way to a degree of caution. The animal carried food to its mouth easily without ataxia of the involved hand, though when its attention was turned elsewhere, the monkey would occasionally drop the morsel it was holding. Grooming activities were performed deftly and while there was difficulty in manipulating very small bits of peanut, whole kernels were scooped up well.

After complete section of the fillet, placing and hopping reactions were permanently absent in the contralateral limbs whether or not the dentato-thalamic fibers were also involved. "Voluntary" grasp, as distinguished from forced grasping, such as follows lesions of the premotor cortex, was also absent in the affected limbs. When the examiner's finger was placed in the animal's hand it responded by grasping only on the normal side. The retention or loss of the placing and hopping and grasp reflexes proved to be a valuable clinical index of the completeness of the procedure interrupting the mesial fillet.

The stab severing the lemniscus also destroyed lateral reticular substance in the midbrain. This interruption of descending autonomic pathways was manifested clinically by the development of a homolateral piloparalysis. This appeared from one to four months after the operation. When the animal was chased or otherwise frightened, the hair on the opposite side of the body ruffed up while that on the homolateral side remained flat with a sharp midline demarcation. Horner's syndrome was never observed in either chim-

panzees or monkeys. The pupil on the operated side was generally larger, due presumably to injury to third nerve fibers.

Discussion

The findings show that in chimpanzees and monkeys a considerable degree of skill in weight discrimination and general propioceptive ability may be regained after section of the contralateral medial lemniscus. This is surprising because the fillet is regarded as the great afferent pathway carrying proprioceptive impulses from the gracile and cuneate nucleii to the thalamus. That such recovery of function may be mediated through the dentato-rubro-thalamic tract is suggested by the fact that when the operative lesion involved both the fillet and the adjacent crossed fibers of the brachium conjunctivum little improvement ensued. Despite the large projections received from the posterior columns, it is generally accepted that the cerebellum subserves only unconscious proprioceptive adjustments. Even with large cerebellar defects in man, conscious proprioceptive sensation remains intact and Holmes (4) found no disturbance in the faculty of appreciating and discriminating weights in patients with cerebellar injuries. Similarly in our own experiments, primary section of the superior cerebellar peduncle produced no diminution in the ability of monkeys to discriminate weights even though the performance was handicapped by ataxia and intention tremor. It would appear that cerebellar fibers are concerned in the maintenance of the function of weight discrimination and may compensate after interruption of the pathway normally mediating conscious proprioceptive impulses.

Clark (1) and Walker (8) have pointed out the close anatomic association of the medial lemniscus and dentato-rubro-thalamic tracts. They constitute separate fiber systems which terminate in close juxtaposition but discretely in the latero-ventral thalamic nucleus. Ferraro and Barrera (3) have recognized the physiological significance of this dual proprioceptive system at a lower afferent level. These authors found that in monkeys, greater disability was produced by sectioning the fasciculus cuneatus than by destroying the nucleus cuneatus. This was explained by the fact that the interruption of the column cut off fibers destined for both the cerebellum and mesial fillet while the nuclear lesion involved only fillet connections and spared the cerebellar fibers.

It is also of interest to compare the findings with those observed after cortical lesions. It has been demonstrated (1, 2, 8) that there is a double projection of thalamic-cortical fibers. The area of the latero-ventral thalamic nucleus that receives the fibers of the medial lemniscus is the source of the relay to the postcentral gyrus, while the region of the ending of the cerebellar fibers sends impulses to the precentral area. With lesions of the frontal lobe in man (8), retrograde degeneration occurred in the contralateral dentate nucleus. Studies from this laboratory (6, 7) have shown that the postcentral gyrus may be removed in primates without lasting impairment in

the ability to discriminate weights or degrees of roughness. Even after ablation of the parietal lobe in monkeys and chimpanzees, a considerable degree of function could be regained with sufficient lapse of time and retraining. The failure of postcentral ablation to produce a significant deficit, corresponds to the result of medial lemniscus section, and bears out Head's dictum that the thalamus does not play a major role in the recovery of proprioceptive function after parietal lesions. Parietal lobectomy is somewhat more effective in producing a deficit than mesial fillet interruption. This is explicable on the grounds that the posterior parietal lobule is in communication with both ascending sensory systems (Ruch, personal communication). It is likely then, that fibers of cerebellar origin may subserve the recovery of proprioceptive function following parietal lesions as they do at lower levels of the central nervous system.

Conclusions

1. Section of the medial lemniscus in monkeys and chimpanzees did not produce an enduring loss of proprioceptive skill in the ability of trained animals to discriminate weights.

2. Primary section of the superior cerebellar peduncle carrying dentato-thalamic fibers produced no significant alteration in weight discrimination.

3. When lesions of the medial lemniscus also involved the crossed dentato-rubro-thalamic tract, there was a marked permanent loss in general proprioceptive function and the ability to discriminate weights.

4. It is suggested that the cerebellar projections to the thalamus may subserve the recovery of proprioceptive function following interruption of the medial lemniscus.

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EXCITATION AND INHIBITION OF PHRENIC MOTOR NEURONES*

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STUDIES of the activities of individual respiratory motor neurones by Adrian and Bronk (1928), Bronk and Ferguson (1935) and Gesell, Atkinson and Brown (1941) have shown that inspiratory activity in both phrenic and intercostal motor units is graded in three ways: by variation in the frequency of discharge of the several motor units; by variation in the numbers of motor units active; and by duration of activity of motor units. From these studies certain inferences have been made as to the nature of the discharge of neurones making up the respiratory center, though of course these neurones lie one or more levels upstream from the ones whose behavior was actually characterized. The localization of the respiratory center, and its differentiation into inspiratory and expiratory divisions (Pitts, Magoun and Ranson, 1939a; Beaton and Magoun, 1941; Pitts, 1941) make possible a study of the behavior of respiratory motor neurones under controlled excitation of the centers. The hope that such a study would add further to an understanding of the functions of the respiratory center and the respiratory motor neurones as well, prompted the present investigation.

METHODS

Our experiments have been performed on cats anaesthetized with 30 mg. per kg. of nembutal intravenously, supplemented as needed with additional small doses. All studies have been made on units dissected from the third cervical root of the phrenic nerve. If a sufficient length of nerve could be exposed, the fourth root was spared, otherwise it was sacrificed. The nerve was carefully and repeatedly split until only one or two fibers remained active within the strand under observation. Potentials were amplified by a condenser coupled amplifier and recorded on bromide paper with a G. E. mirror oscillograph. The animal was maintained in a warmed and humidified shielding box. The respiratory center was stimulated through bipolar needle electrodes oriented in the Horsley-Clarke stereotaxic instrument, the stimuli being brief repetitive condenser discharges (time constant approximately 0.1 msec.), independently variable as to frequency and intensity. Respiration was recorded by a light rubber optical tambour recording pressure changes within a five gallon bottle connected through a soda lime tube to the tracheal cannula. The system was filled with oxygen and except during the taking of records was constantly replenished by opening to a rubber bag oxygen reservoir.

RESULTS

Nature of phrenic neurone activity

During the inspiratory phase of eupneic respiration, phrenic neurones respond repetitively with a slowly augmenting frequency of discharge, which suffers sudden decrement as expiration begins. A certain number of neurones are active throughout the inspiratory cycle, as is the neurone of

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the ability to discriminate weights or degrees of roughness. Even after ablation of the parietal lobe in monkeys and chimpanzees, a considerable degree of function could be regained with sufficient lapse of time and retraining. The failure of postcentral ablation to produce a significant deficit, corresponds to the result of medial lemniscus section, and bears out Head's dictum that the thalamus does not play a major role in the recovery of proprioceptive function after parietal lesions. Parietal lobectomy is somewhat more effective in producing a deficit than mesial fillet interruption. This is explicable on the grounds that the posterior parietal lobule is in communication with both ascending sensory systems (Ruch, personal communication). It is likely then, that fibers of cerebellar origin may subserve the recovery of proprioceptive function following parietal lesions as they do at lower levels of the central nervous system.

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the control record of Fig. 3. Others come into activity for a brief interval only near the peak of inspiration (control record, Fig. 1). As Gesell, Atkinson and Brown (1941) have pointed out, increase in frequency of discharge and successive recruitment during development of inspiration, release additional inspiratory energy smoothly as it is needed (control record, Fig. 5). Only a fraction of the phrenic neurones, however, is active during eupneic respiration and the discharge frequencies which they attain are relatively low.

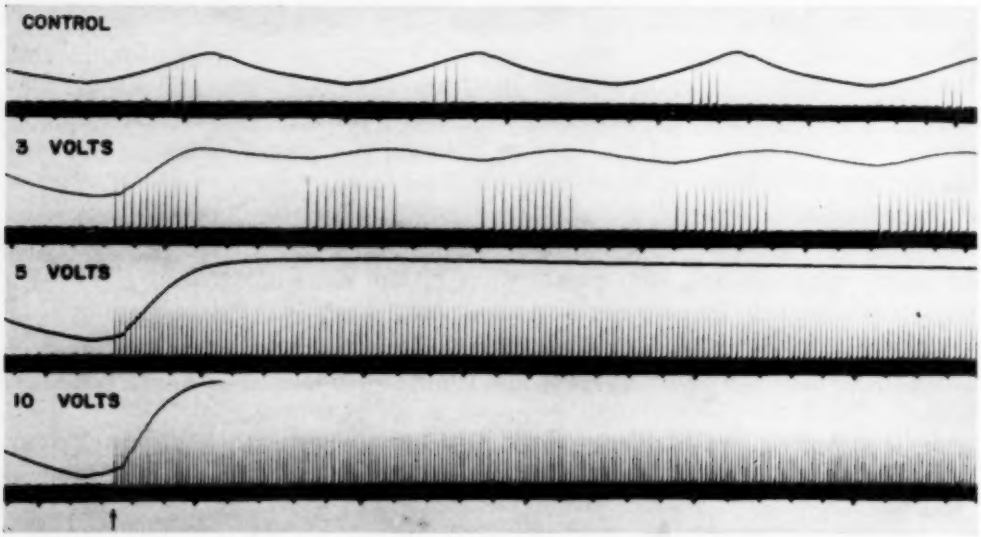

FIG. 1. Impulses discharged by a single phrenic neurone and respiratory response on stimulation of the inspiratory center with stimuli at a frequency of 220 per sec. and intensities of 3, 5, and 10 V. Arrow marks beginning of stimulation. Time, $\frac{1}{5}$ sec.

Thus there exists a large reserve of inspiratory energy which may be drawn against under conditions of respiratory stress. Such conditions of stress may be simulated by electrical shocks at controlled intensities and frequencies applied to the respiratory center.

Effect of inspiratory center stimulation on phrenic neurone discharge

Stimulation of the inspiratory center with repetitive shocks of high frequency and moderate intensity (240 per sec.; 8 volts) leads to maintained deep inspiration involving both thorax and diaphragm to an essentially maximal degree (Pitts, Magoun and Ranson, 1939a). The neural basis for this respiratory response is illustrated in part by the behavior of the phrenic neurone in the lower records of Fig. 1. Stimuli of an intensity of 5 or 10 V. and a frequency of 220 per sec., applied to the inspiratory center at the time indicated by the arrow at the bottom of the records, led to repetitive discharge of the phrenic neurone and deep inspiration, both maintained for the duration of stimulation.

Factors controlling magnitude of inspiratory response

A. Stimulus intensity. It is apparent from inspection of the records of Fig. 1 that both the response frequency of the phrenic neurone and depth of inspiration are related to stimulus intensity. At intensities of 4 v. or more, phrenic neurone discharge was constant and the respiratory trace showed no phasic movements. At intensities of 2 and 3 v., however, the response of the neurone was interrupted and the respiratory trace, though shifted towards a

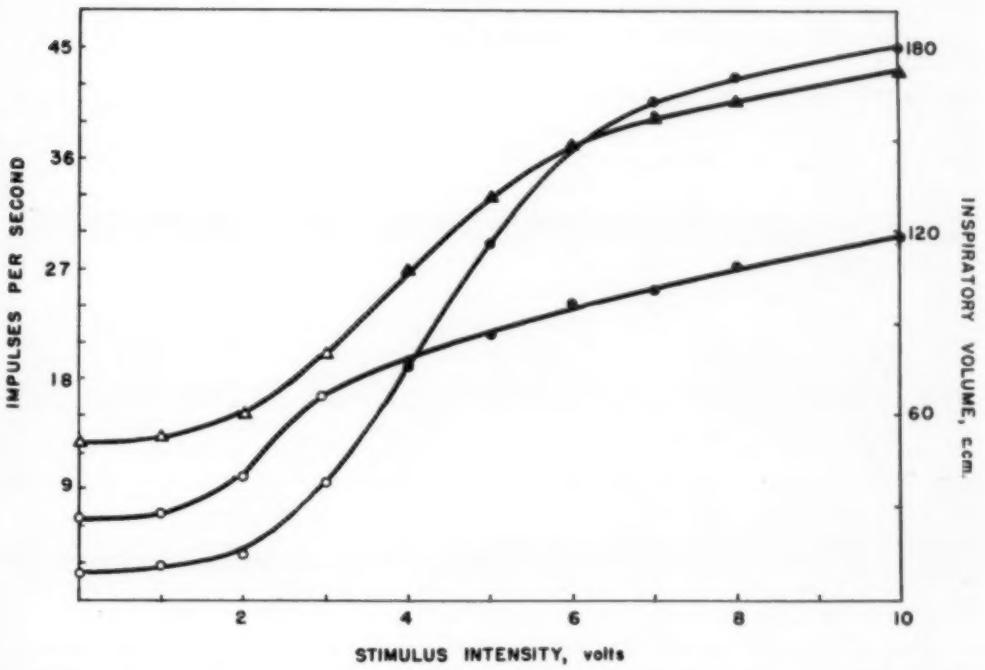

FIG. 2. Relation between the discharge of impulses by phrenic neurones, volume of inspiration and intensity of stimulation of the inspiratory center. Triangles, inspiratory volume in c. cm. measured from the level of the preceding normal expiration. Circles, impulses discharged per sec. by two phrenic neurones. Frequency of inspiratory center stimulation, 220 per sec. throughout; intensities as indicated. Hollow symbols indicate a response showing repiratory modulation; solid symbols indicate a maintained uninterrupted response.

position of inspiration, showed definite respiratory waves. An intensity of 1 v. approximated threshold, for both respiratory response and phrenic neurone discharge showed minimal augmentation.

Quantitation of the entire series of records of which Fig. 1 is but a part, yields Fig. 2. The response of first one and then a second phrenic neurone was determined to intensities of stimulation from 1 to 10 v. Stimulus frequency was kept constant throughout at 220 per sec. and the position of the electrodes was unchanged. The responses of these two phrenic neurones in terms of impulses per sec. are plotted in the lower two curves as

circles. The respiratory responses, identical of course in the two series of tests, are plotted in the upper curve as triangles. They represent depth of inspiration, in cubic centimeters, from the preceding normal expiratory level. The use of hollow symbols indicates that respiration continued rhythmic, while the solid symbols at intensities of 4 v. or more represent maintained inspiration.

The characteristic relationship between stimulus intensity and either frequency of phrenic nerve impulses or depth of inspiration is sigmoid in form. However, the two neurones of Fig. 2 do not behave in an identical manner to an increase in stimulus intensity, nor does the response of either

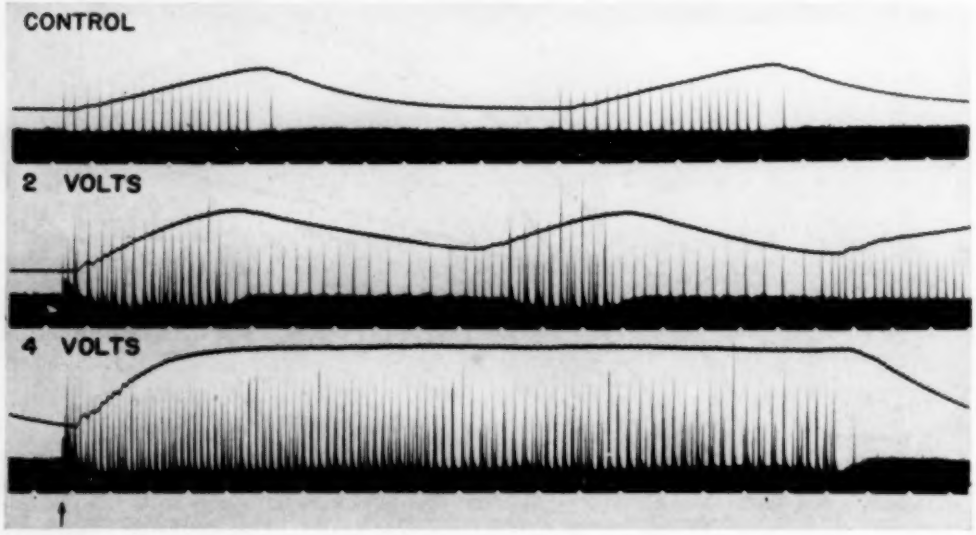

FIG. 3. Impulses discharged by two phrenic neurones and respiratory response on stimulation of the inspiratory center with stimuli at a frequency of 220 per sec. and intensities of 2 and 4 v. Arrow marks beginning of stimulation. Time, $\frac{1}{5}$ sec.

reflect at all accurately the inspiratory volume curve. The essential features of these curves have been duplicated in five other experiments, though magnitudes and slopes vary. In general, an intensity of one volt is near threshold, the greatest change in response occurs between 3 and 6 v., and at higher intensities both inspiratory volume and frequency of impulses tend to level off. Obviously, inspiratory volume is related to frequency of discharge of the several motor neurones. However, individual neurones vary so widely in their behavior to stimuli of a given intensity, that agreement between volume and frequency curves might reasonably be expected only if one averaged the response of many neurones.

Even so, agreement would not be perfect for, as is evident from Fig. 3, numbers of neurones active, as well as the degree of activity of each, determine the inspiratory response. The preparation from which Fig. 3 was obtained consisted of two functional neurones, of which only one was spon-

taneously active. Stimulation of the inspiratory center at high frequency (220 per sec.) and low intensity (2 v.) recruited the previously inactive neurone characterized by greater spike potential. In addition, the discharge frequency of the previously active neurone was increased somewhat and its activity prolonged throughout the respiratory cycle though at a reduced frequency during expiration. As a consequence of the operation of such factors, inspiration increased in depth and a shift of respiratory mid-position toward the inspiratory side occurred. Increasing the intensity of stimulation to 4 v. increased frequency of discharge of both neurones, maintained their activities constant, and further increased inspiratory depth. Quantitation of such results is difficult for if more than two neurones are active, it becomes almost impossible to distinguish with certainty their individual impulses. However, it has been observed that there is a wide range of stimulus intensity over which additional neurones are recruited. Thus in Fig. 2, even at the highest intensities, it is probable that a portion of the inspiratory increment resulted from recruitment of additional neurones as well as from an increased frequency of discharge of those already active.

B. Stimulus frequency. If the intensity of stimulation is maintained constant and the frequency varied, results qualitatively similar to those shown in Fig. 1 and 2 are obtained. A plot of such an experiment is shown in Fig. 4, in which the behavior of first one and then a second phrenic neurone was determined to stimuli of an intensity of 8 v. and frequencies from 6 to 220 per sec. The significance of the various symbols is the same as in Fig. 2.

Both the frequency of phrenic nerve impulses and depth of inspiration increase with increasing stimulus frequency. The relationship like that for stimulus intensity is a sigmoid one. Qualitatively similar results have been obtained in four additional experiments, though magnitudes are dissimilar. By chance, no doubt, the behavior of one of the neurones of Fig. 4 approximates quite closely the inspiratory volume curve, though the other plateaus quite early in the frequency series. Again, correspondence between inspiratory volume and impulse frequency might be expected only on the basis of the average response of many neurones. As with stimulus intensity, an increase in stimulus frequency leads to the recruitment of additional neurones, and it is probable that the inspiratory increments of Fig. 4, even at the highest stimulus frequencies are in part the result of such recruitment.

The results just presented may be summarized as follows. Stimulation locally within the inspiratory center of more units, by increasing stimulus intensity, or of a given number of units at higher frequency, leads to an increased rate of discharge and recruitment of phrenic motor neurones. Such a view implies multiplicity of excitatory pathways between inspiratory center and any given final motor neurone. The degree of excitation of the neurone, as measured by the frequency at which it fires, is dependent then on the average number of impulses impinging on it from these many sources. Those neurones which are normally quiescent receive subliminal excitation (*vide infra*), but may be brought into activity by increasing either numbers of

pathways active or the frequency at which they transmit impulses. Low intensity or low frequency stimuli sum with spontaneous impulses from the inspiratory center and cause less excitable motor neurones to become active earlier in the inspiratory cycle. The inhibitory mechanisms which normally serve to interrupt spontaneous inspiratory activity (Pitts, Magoun and Ranson, 1939c) likewise inhibit this augmented discharge, so rhythmic res-

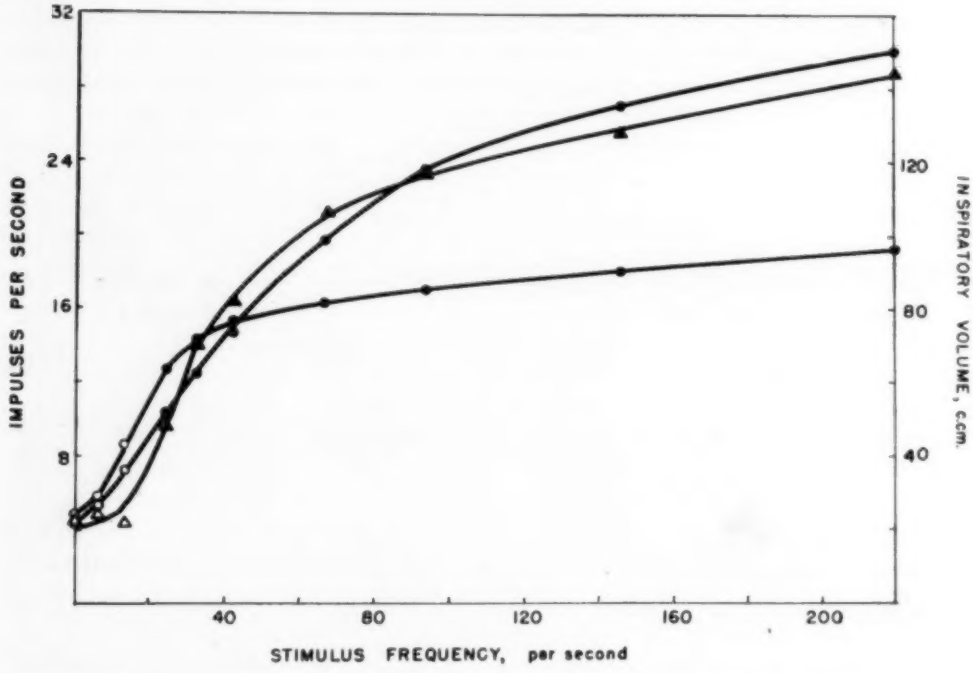

FIG. 4. Relation between the discharge of impulses by phrenic neurones, volume of inspiration and frequency of stimulation of the inspiratory center. Significance of symbols the same as Fig. 2. Intensity of inspiratory center stimulation, 8 v. throughout; frequencies, as indicated.

piration continues. But more intense or more frequent stimuli continue the process of prolongation of period of activity to its ultimate end, namely, continuous uninterrupted discharge whose frequency is a function of frequency and intensity of stimulation. Inhibitory mechanisms no longer can interrupt this intense discharge of the inspiratory center and maintained deep inspiration results.

Effect of expiratory center stimulation on phrenic neurone discharge

The behavior of phrenic neurones on stimulation of the expiratory center is in many ways the exact opposite of that on inspiratory center stimulation. In the control record of Fig. 5 two neurones which may be distinguished by differences in magnitude of spike potential, are active, one throughout the

inspiratory cycle, the other only at the peak of inspiration. Stimuli of an intensity of 2 and 4 v. and a frequency of 220 per sec. were applied to the expiratory center at the time indicated by the arrow, and maintained for the remainder of the record. The less intense stimuli inhibited activity of the neurone of greater spike potential and reduced frequency of discharge and duration of the period of activity of the other neurone. The more intense stimuli inhibited activity of both neurones completely. Still higher intensities served only to convert passive into active expiration. These results have been duplicated in all essential features by increasing frequency of stimulation at constant intensity.

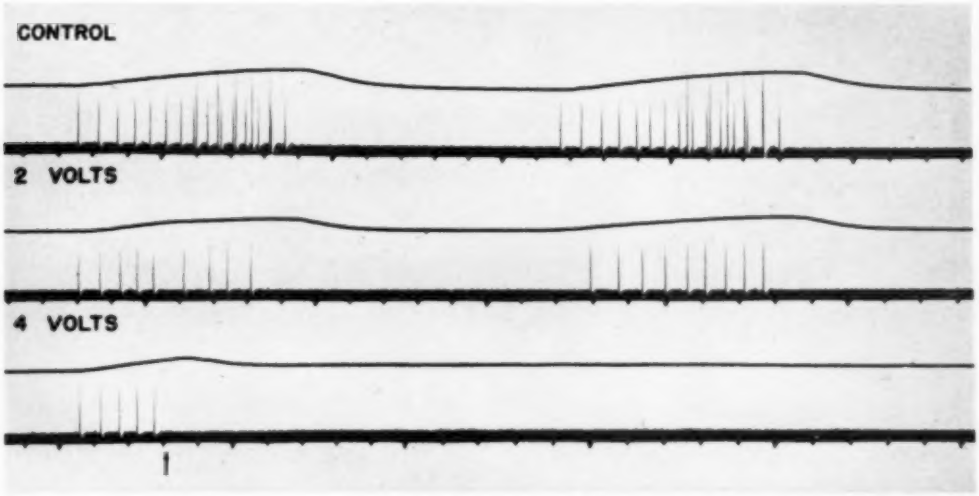

FIG. 5. Impulses discharged by two phrenic neurones and respiratory response on stimulation of the expiratory center with stimuli at a frequency of 220 per sec. and intensities of 2 and 4 v. Arrow marks beginning of stimulation. Time $\frac{1}{4}$ sec.

A comparison of Fig. 5 with Fig. 3 illustrates well the contrasting results on phrenic nerve discharge of expiratory and inspiratory center stimulation: "decruitment" as opposed to recruitment; decreased frequency of discharge as opposed to increased frequency; shortened duration of activity as opposed to prolonged; and finally with more intense stimuli, complete inhibition as opposed to continuous activity.

Connections between neurones of inspiratory and expiratory centers

Each of the two divisions of the respiratory center has an extent of over 30 c. mm. within the reticular formation of the medulla, yet the stimulation of but a small fraction of either leads to an essentially maximal respiratory response (Pitts, Magoun and Ranson, 1939a). It has been shown that a stimulus of 8 v. excites medullary structures only within a radius of 0.5 mm. around the tips of bipolar needle electrodes (Pitts, 1941), yet such a

stimulus applied to the inspiratory center at a frequency of 240 per sec. may produce an inspiration some ten times the normal tidal volume. Such experiments as well as more direct ones (Pitts, Magoun and Ranson, 1939b), indicate that the neurones making up the centers are extensively interconnected.

The general method utilized in performing our experiments throws additional light on the interconnection of the component units of the centers. Routinely single active fibers have been isolated from the phrenic nerve,

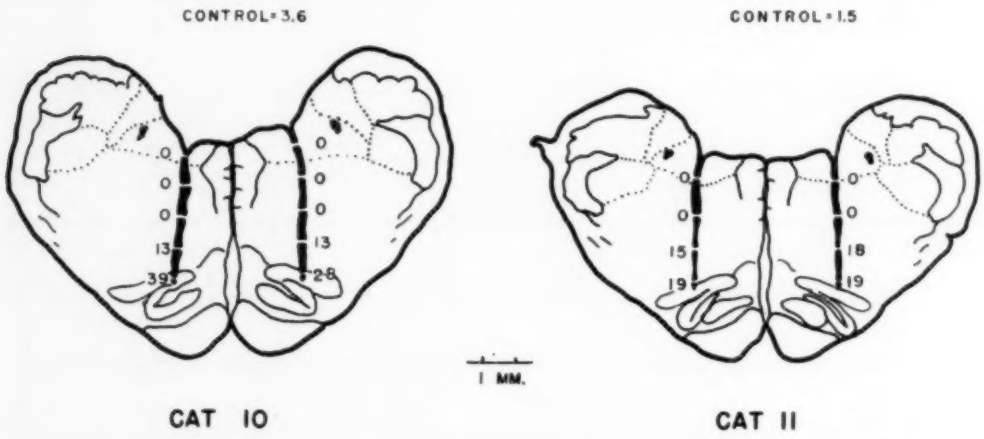

FIG. 6. Tracings of stained sections of the medulla oblongata of the cat showing electrode position and frequency of discharge of single phrenic neurones during stimulation at each level. Heavy vertical lines indicate track of the stimulating electrodes; the interruptions of the line, the position of the bare electrode tips. Numbers opposite electrode positions indicate frequency of discharge of a single phrenic neurone in impulses per sec. during stimulation. Control values above, give the frequency of spontaneous discharge in impulses per sec. Two separate experiments are shown. Stimulation at all levels in both experiments, 8 v. and 220 per sec.

the electrodes have then been placed within the general confines of the centers as previously outlined, either ipsilateral or contralateral to the phrenic fiber recorded from. In all instances, providing the electrode was accurately placed within the center, stimulation of the expiratory center inhibited, and stimulation of the inspiratory center excited that specific phrenic neurone chosen entirely at random. Fig. 6 (cats 10 and 11) shows the results in two experiments of stimulation of both sides of the medulla at millimeter intervals with stimuli of an intensity of 8 v. and a frequency of 220 per sec., recording the activity of a single phrenic fiber split off from the left nerve. The spontaneous activity in impulses per sec. is shown as the control value above the tracing. The heavy black lines interrupted at millimeter intervals show the successive levels of penetration of the needle electrode. The effect of stimulation at each level is indicated by the number opposite the break in the line, representing the frequency of impulse discharge per sec. Out of several experiments performed these two were chosen for presen-

tation, for at each position of the electrodes the respiratory response was maintained constant, uninterrupted by rhythmic respiration. Thus at those levels marked with a zero, complete inhibition of activity was obtained, while at the levels marked by numbers, continuous discharge at the indicated frequency resulted. It is evident that a given phrenic neurone may be activated or inhibited from widely separated regions of the reticular formation of both sides of the medulla. While cat 10 showed a somewhat greater response of the single left phrenic neurone from stimulation of the most ventral level on the left side of the medulla, in general there has been no uniformly greater ipsilateral response. Since descending connections between inspiratory center and phrenic neurones are almost entirely if not completely uncrossed (Pitts, 1940), it follows that component units of the centers are connected and that stimulation of a few may activate many or all. In addition, equally extensive connections of an inhibitory type must exist between the two centers, for activation of a millimeter cube of the expiratory center leads to inhibition of the entire inspiratory center.

The experiments just presented indicate that the neurones making up both the inspiratory and the expiratory centers are richly interconnected. The latter exerts an inhibitory action on the inspiratory center, reducing the frequency and possibly the number of those neurones in activity. The withdrawal of excitation from phrenic motor neurones leads to cessation of their discharge and passive expiration. Active expiration probably results from more intense excitation of the expiratory center and consequent activation of expiratory intercostal motor units.

Characteristics of the excitatory process

In the preceding sections the general relationship between controlled excitation applied to the two divisions of the respiratory center and phrenic neurone activity have been presented. More detailed knowledge is obtained by closer examination of the relation between stimulus and response. For this purpose phrenic neurones have been chosen which were not spontaneously active, so as to eliminate confusion of spontaneous impulses with the response to a specific stimulus. Records have been taken at higher paper speeds in order to separate stimulus artifact and impulse satisfactorily. In Fig. 7 are presented the results of stimulation of the right side of the inspiratory center on the discharge of a phrenic neurone dissected from the contralateral phrenic nerve. The stimulus frequency was maintained at 14 per sec. and the intensity varied between 4 and 12 v. The stimulus artifact is barely visible as a fine line spaced at regular intervals throughout each record. At an intensity of 4 v. the neurone did not respond; at 6 v. the response occurred only during a part of the inspiratory cycle; at 8 v., throughout inspiration and occasionally in expiration. At an intensity of 12 v. the neurone responded to every stimulus throughout the whole respiratory cycle. It is evident that the neurone responds when it does so at all with a relatively fixed latency following a given stimulus. The latency

varies between 8 and 16 m. sec. This variation in latency has almost the appearance of being a random one; certainly it is not related to stimulus intensity. But there is a tendency for it to be somewhat shorter early in inspiration and to be longer in the expiratory phase. In general the picture is one of summation of subliminal excitation delivered to the phrenic neurone during inspiration with volleys of impulses synchronous with stimuli to

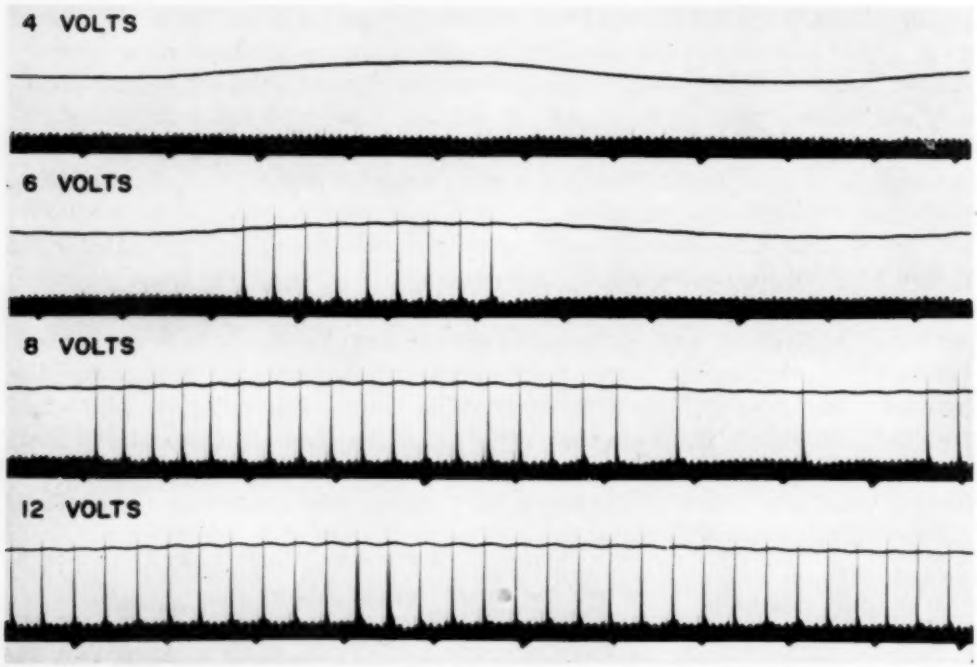

FIG. 7. Impulses discharged by a single phrenic neurone during stimulation of the inspiratory center at a frequency of 14 per sec. and intensities of 4, 6, 8 and 12 v. This neurone normally showed no spontaneous activity. Stimulation was continued throughout each record. Stimulus artifact barely visible as a faint trace at regular intervals in all records.

the inspiratory center. At the highest intensity, these volleys are themselves of sufficient magnitude to excite not only during inspiration but also during expiration as well. The latency of the response is a composite of phrenic nerve conduction time, synaptic delay at the phrenic neurone and at whatever internuncials may be involved, spinal cord conduction time, and conduction time and delay within the center. These several contributions have not been individually assessed as yet. These facts seem evident: (i) that this neurone, though inactive normally, is receiving subliminal excitation; (ii) that each stimulus to the inspiratory center is followed by a synchronous volley of impulses, sufficient at intensities of 6 v. or more to trigger the neurone and cause it to fire an impulse; and (iii) that the magnitude of this

volley is related to stimulus intensity and at 12 v. is capable of exciting even during the expiratory phase when background activity is at a minimum.

Additional light is cast on the nature of the normal activity of the inspiratory center by studying the response of phrenic neurones to stimuli of constant intensity and varying frequency. In Fig. 8 is presented the result of stimulation of the inspiratory center with stimuli of an intensity of 8 volts

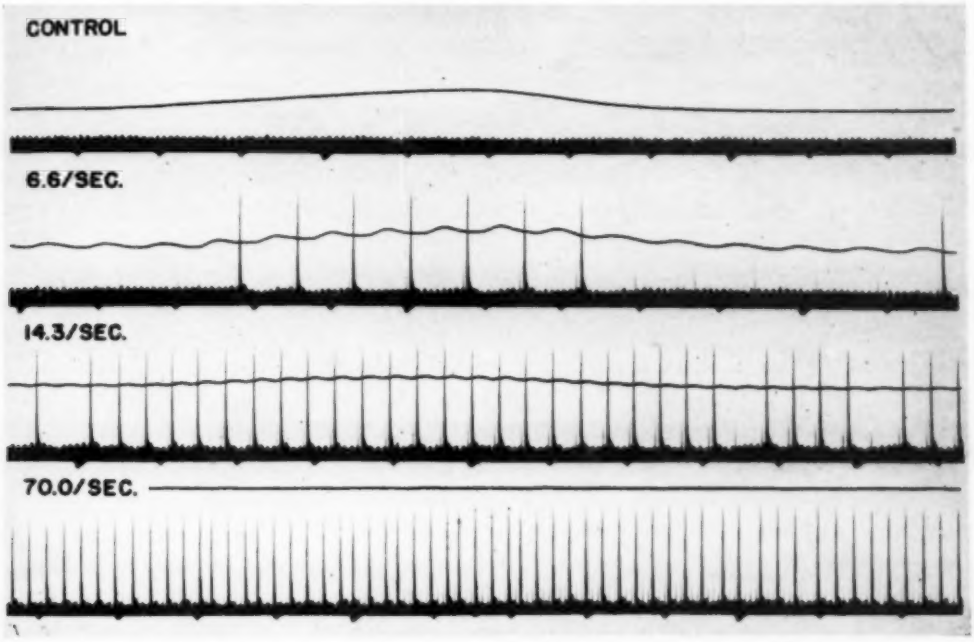

FIG. 8. Impulses discharged by a single phrenic neurone during stimulation of the inspiratory center at an intensity of 8 v. and frequencies of 6.6, 14.3 and 70 per sec. This neurone normally showed no spontaneous activity. Stimulation continued throughout each record. Stimulus artifact barely visible as a faint trace at regular intervals in all records.

and frequencies of 6.6, 14.3 and 70 per sec. At a frequency of 6.6 stimuli per sec. some seven stimuli were effective during inspiration while the five falling within the expiratory cycle were ineffective in eliciting an impulse. Increasing the frequency to 14.3 without altering intensity rendered most of the stimuli effective during both inspiration and expiration, though during the latter phase an occasional impulse was dropped. At both frequencies each impulse follows a given stimulus with a latency of from 8 to 15 m sec. It seems probable at the lower frequency of stimulation that each volley of impulses resulting from a stimulus sums with subliminal excitation delivered to the phrenic neurone during spontaneous activity of the inspiratory center, and triggers an impulse. But it would also appear that each stimulus leaves

in its wake a residuum of excitation* which persists long enough for stimuli at the higher frequency to facilitate succeeding ones. Accordingly stimuli trigger impulses throughout the expiratory cycle even though normal background activity is minimal. At a frequency of 70 per sec. the same triggering of impulse by stimulus is noted, the latency being essentially the same as at the lower frequencies. On an average, however, only every third stimulus is effective, although every fourth or every second occasionally triggers an

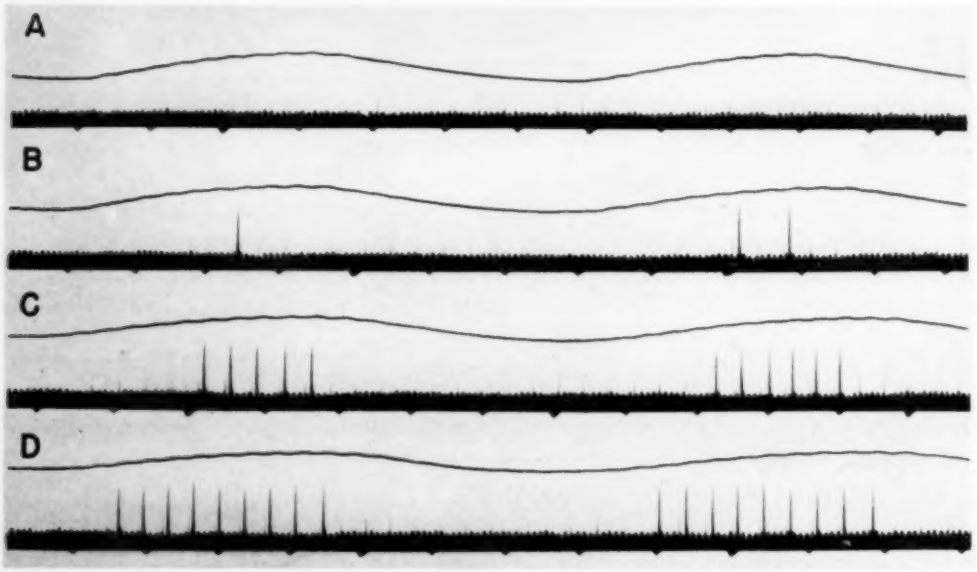

FIG. 9. Impulses discharged by a single phrenic neurone during stimulation of the inspiratory center at a frequency of 14 per sec. and an intensity of 4 v. A to D, progressive increase in chemical stimulus to respiration produced by rebreathing oxygen after removal of the carbon dioxide absorption tube. This neurone showed no spontaneous activity either normally or after rebreathing.

impulse. Certain volleys of impulses set up by stimuli succeeding each other at such short intervals find the motor neurone relatively refractory and fail to trigger it. At such a frequency the activity of the inspiratory center is so completely dominated by stimulation that the discharge of the phrenic neurone is continuous, and respiratory rhythm is lost. Frequency of firing of the neurone is then determined by the level of excitation maintained by the continued volleys of impulses from the inspiratory center and the rate of recovery of excitability of the neurone once it has discharged an impulse. At higher stimulus frequencies the neurone fires at a higher rate but not in proportion to the increase in frequency. The rate of firing at 70 per sec. was

* While this might mean a persisting change initiated by a given impulse at a synapse, it is more logical in view of delay pathways through internuncials and between neurons making up the center to consider that it represents a temporally dispersed volley of impulses.

25, approximately 3 to 1; at 220 per sec. it was 38, approximately 6 to 1. Tripling stimulus frequency probably falls short of tripling the number of impulses per sec. delivered to the phrenic neurone. Also the degree of subnormality of the neurone may be increased by the increased rate of firing. Both factors would tend to reduce proportionality between stimulus and impulse frequency. The results presented above apply equally well to neurones which show spontaneous activity, although they are less apparent because of the interpolation and interference of spontaneous impulses.

A third type of experiment gives additional information on the character of the normal excitation of phrenic neurones by the inspiratory center. Stimuli of an intensity of 4 v. and a frequency of 14 per sec. failed to excite the neurone studied as shown by record A of Fig. 9. The same stimulus intensity and frequency were maintained throughout all records from A to D. Carbon dioxide was allowed to accumulate in the inspired gas by removal of the soda lime absorption tube. Records B to D illustrate the effects of a progressive increase in chemical stimulus coupled with a constant electrical stimulus. The stimuli applied to the inspiratory center reach threshold and fire the neurone over a progressively increasing period of the inspiratory cycle as activity of the inspiratory center is increased by the chemical stimulus. It is logical to assume that under normal conditions (record A) subliminal excitation from the inspiratory center and subliminal volleys resulting from stimuli still did not reach threshold proportions; hence the neurone did not fire. Increasing excitation from the inspiratory center by increasing the carbon dioxide tension of the inspired gas enabled the volleys to reach threshold and trigger impulses earlier and earlier in the inspiratory cycle. At no time, however, during this series was normal excitation sufficient to cause the neurone to fire spontaneously.

Summary

Low intensity or low frequency electrical stimulation of the inspiratory center reproduces the same effects on phrenic neurone discharge as normal chemical activation of the respiratory center, namely: increased frequency of discharge; increased duration of activity; and recruitment of inactive neurones. Stimulation of the expiratory center, on the other hand, produces exactly the reverse effects, namely: decreased frequency of discharge; decreased duration of activity; and reduction of numbers of active neurones. Results obtained on varying stimulus intensity or frequency indicate that each phrenic motor neurone receives excitation from the inspiratory center over a number of separate pathways. The average level of excitation of the neurone is dependent upon the number of these pathways functioning and the frequency at which they transmit impulses. The rate at which the neurone fires is a function of its level of excitation and the time course of recovery of excitability once it has discharged an impulse. The inspiratory center-phrenic neurone system to this extent is similar in behavior to the hypothalamus-sympathetic motor neurone system described by Pitts, Larrabee and Bronk (1941) and Pitts and Bronk (1942).

Probably all the neurones making up the phrenic motor pool receive some excitation from the inspiratory center during eupneic respiration though for a large fraction it is of a subliminal degree. Any increase in activity of the neurones of the inspiratory center not only increases the frequency of discharge of those phrenic neurones already active but also recruits previously quiescent ones. Such an increase in activity of the constituent neurones of the inspiratory center may be produced experimentally by increasing either their frequency of discharge or the number active. It is probable that the same mechanisms operate normally under conditions which augment respiration.

Each phrenic neurone is functionally related, at least potentially, with each of the constituent neurones of the inspiratory center owing to their rich synaptic interconnections. Neurones of the expiratory center are similarly interconnected, and by virtue of their inhibitory influence on the inspiratory center, are capable of withdrawing excitation from phrenic neurones. Connections within a center probably serve to synchronize activities grossly with respect to phase of respiration and to facilitate those units inherently less excitable. Connections between centers are mutually inhibitory and prevent simultaneous activity of antagonistic elements.

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